Volume XIX Number 12

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# DISEASES OF THE NERVOUS SYSTEM

*A Practical Journal on Psychiatry and Neurology*

DECEMBER
1958

(Contents on page 508)

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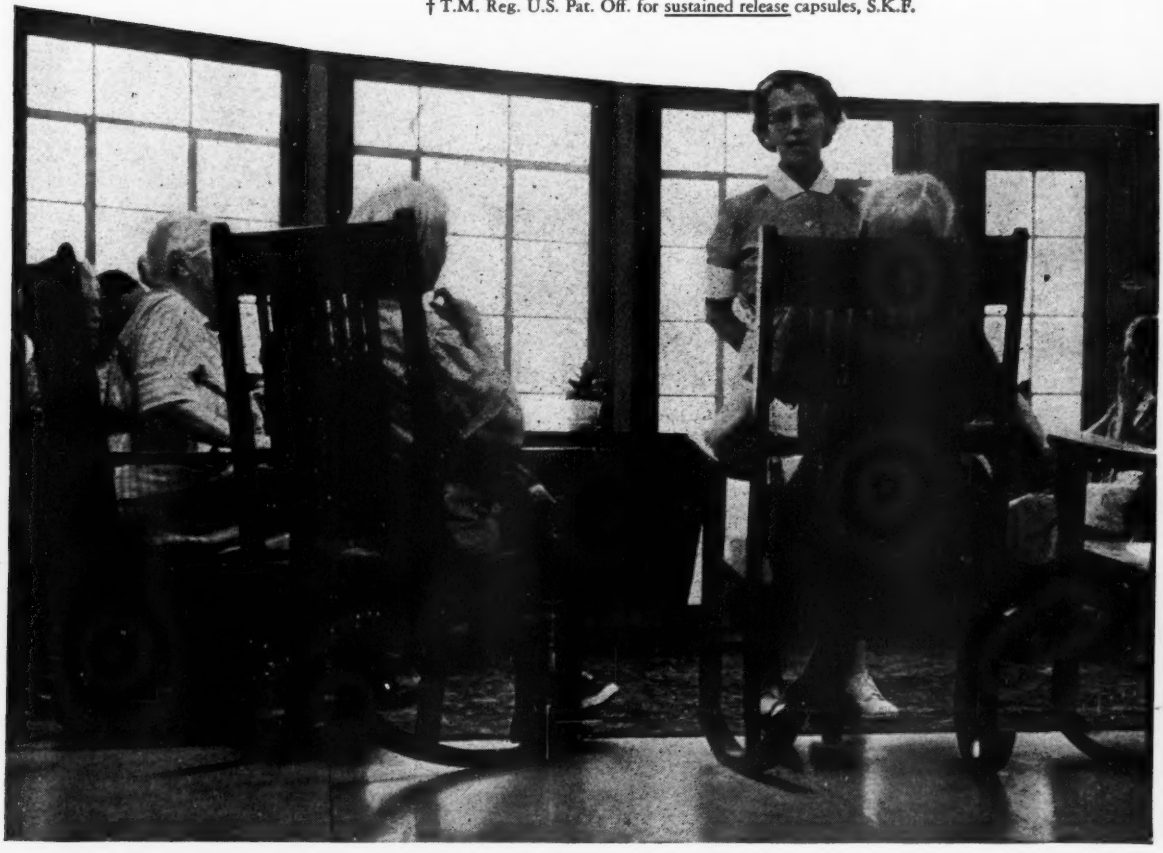

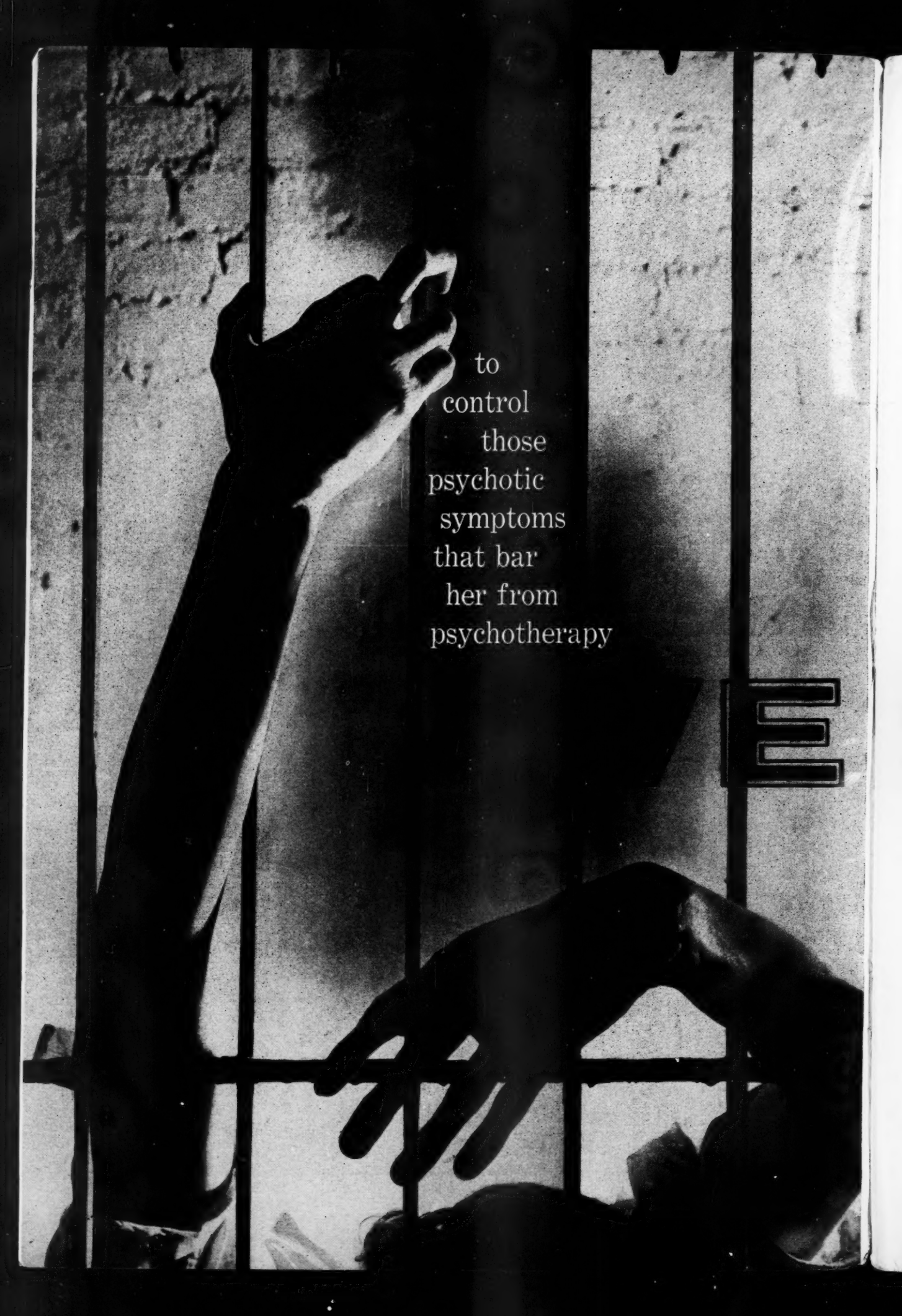
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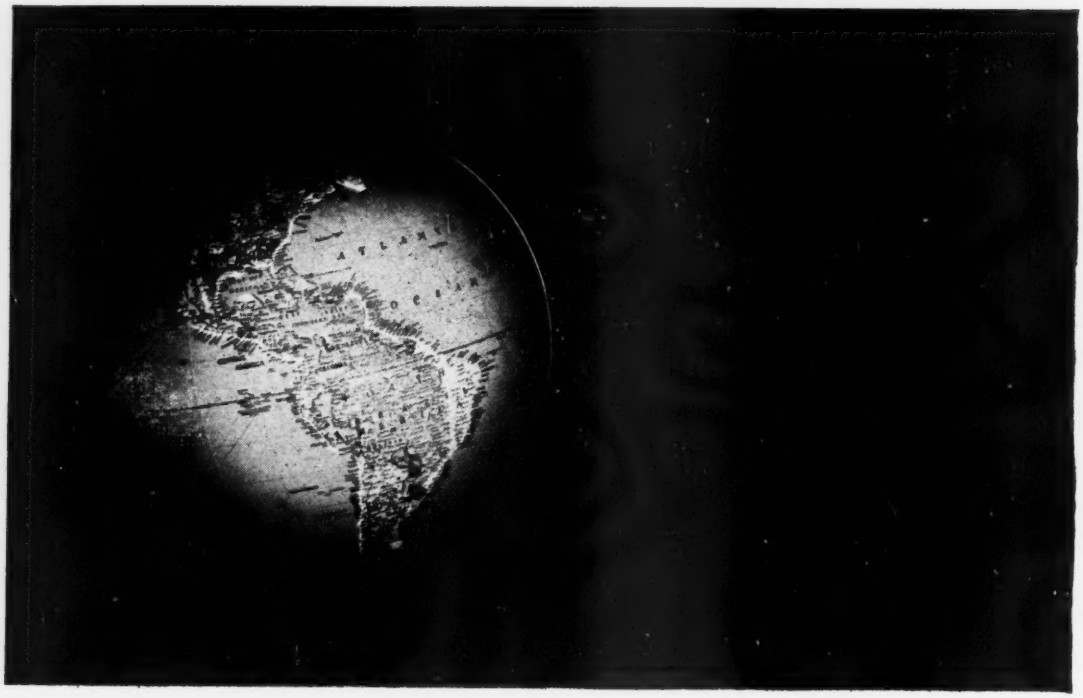

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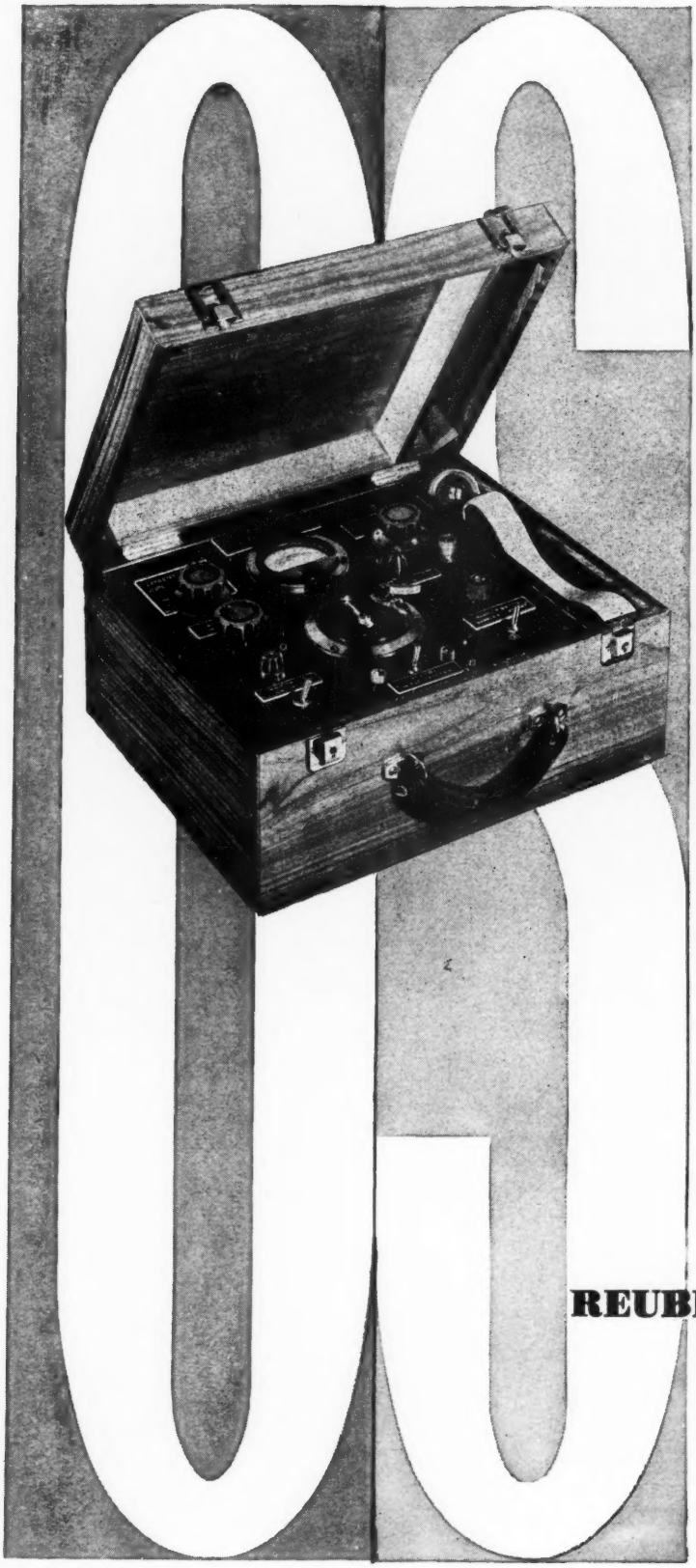

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## Contents

EFFECT OF A CHOLESTEROL LOWERING AGENT ON THE AGED MENTALLY ILL ..... 511
Michael J. Carver, Joseph P. Dailey, Robert L. Colescott and Jackson A. Smith

SCHIZOPHRENIA AS A WORLD PROBLEM ..... 513
James L. McCartney

BRAIN TUMOR PRESENTING AS CONVULSIVE DISORDER ..... 518
Robert R. J. Strobos, Eben Alexander, Jr., and Richard L. Masland

SLEEP TREATMENT IN MENTAL DISORDERS ..... 523
H. Azima

EVALUATION OF PROCHLORPERAZINE AND A PROCHLORPERAZINE-COMBINATION IN DISTURBED PATIENTS ..... 531
Roy C. Noble and Charles W. Castner

NARCO-STIMULATION ..... 534
Albert A. LaVerne

MEETING OF EASTERN PSYCHIATRIC RESEARCH ASSOCIATION, INC. ..... 538

TOXICOLOGY OF MARSILID[R] AND OTHER AMINE OXIDASE INHIBITORS ..... 539
Lowell O. Randall and Robert E. Bagdon

MARSILID TOXICITY ..... 541
Robert J. Floody, Robert E. Dixon and V. D. Mattia, Jr.

IPRONIAZID IN PULMONARY TUBERCULOSIS ..... 545
George G. Ornstein

IPRONIAZID IN ORTHOPEDICS ..... 546
David Bosworth

DISCUSSION: IS MARSILID A DANGEROUS DRUG? ..... 548

SUICIDAL RISK IN A MUNICIPAL GENERAL HOSPITAL ..... 556
Jacob H. Friedman and Remo Cancellieri

PSYCHOMOTOR PAROXYSMS OF NON-EPILEPTIC ORIGIN ..... 562
Eugene Revitch

INDEX ..... 567

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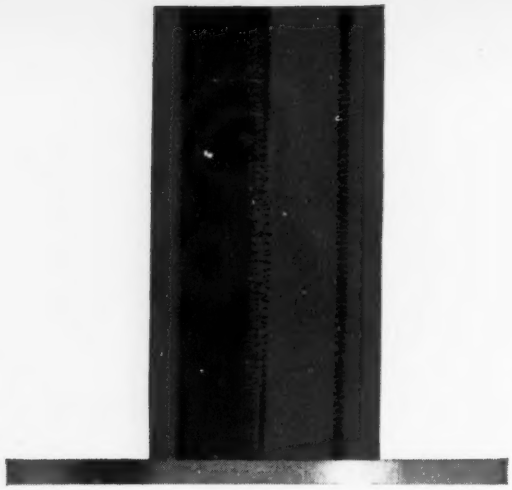

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A PRACTICAL JOURNAL ON PSYCHIATRY AND NEUROLOGY

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# Effect of a Cholesterol Lowering Agent on the Aged Mentally Ill

MICHAEL J. CARVER, PH.D., JOSEPH P. DAILEY, PH.D., ROBERT L. COLESCOTT, B.S., and JACKSON A. SMITH, M.D.

Kinsell, et al.[5,6] in 1952 reported that serum cholesterol was lowered in patients receiving vegetable oils as a source of fat and that when the vegetable oil was removed from the diet the serum cholesterol returned to pre-treatment concentration. This work was later confirmed by Ahrens[1] and by Beveridge[2] and one component of the vegetable oil responsible for this lowering was found by Kinsell[4] to be the ester of linoleic acid, a fatty acid containing eighteen carbon atoms and two double bonds.

A biological relationship between linoleate and pyridoxine, vitamin $B_6$, was indicated in experiments carried out by Birch[3] in 1938. This relationship was further established in rats by the work of Witten and Holman.[7] These latter investigators demonstrated the addition of both pyridoxine and linoleate to the diet of rats deficient in both essential fatty acids and pyridoxine caused a significant increase in body weight compared to the feeding of either material alone. They further demonstrated that the addition of both pyridoxine and linoleate to the doubly deficient diet caused a substantial increase in carcass content of arachidonic acid, an essential fatty acid containing twenty carbon atoms and four double bonds, compared to the feeding of either material in conjunction with the deficient diet.

Even though the mechanism by which these essential fatty acids and pyridoxine influence plasma cholesterol is not completely understood, a stable and palatable emulsion containing a high concentration of linoleic acid and a significant amount of pyridoxine would be expected to be desirable from a therapeutic viewpoint. This paper is a report on the effectiveness of such an emulsion as a suplement to an institutional diet in the treatment of hypercholesterolemia.

## Materials and Methods

The patient group in the study was composed of ten hospitalized mentally ill patients maintained on a general diet during the course of the study. The 40% safflower oil emulsion was administered postprandially in an oral dosage of 4 oz. or 8 oz. daily either undiluted or with water. The preparation was well tolerated and no adverse side effects were noted. Throughout the experiment no attempt was made to restrict or control the intake of fatty food.

Each 4 oz. dose* contained 1.62 mg. pyridoxine hydrochloride and 24.0 g. of refined safflower oil stabilized with 24 mg. mixed tocopherols, 2.4 mg. propyl gallate and 12 mg. citric acid. Sodium benzoate was added to prevent bacterial contamination. The analysis of the oil is as follows: linoleic acid 72.3%, linolenic acid 0.5%, arachidonic acid 0.0%, oleic acid 6.5%, iodine number 142.

The method of Zak[8] was used for the analysis of free and total cholesterol. All determinations were performed in duplicate and agreed within ± 5 mg. %.

Prior to the feeding of the emulsion, two

From the Nebraska Psychiatric Institute, Omaha, Nebraska, and the Research and Development Department of Armour Laboratories, Kankakee, Illinois.

*A 65% emulsion containing these ingredients in the above proportions is now available from Armour Laboratories under the trade name "Arcofac."

determinations of free and total cholesterol were made on each patient to establish a base line. Additional determinations were performed after two and four weeks of treatment. The patients were then continued on their usual diet without fat supplementation. Sixty days after the therapy, cholesterol determinations were once again carried out. Five of the patients were retested using 5 oz. of the 65% emulsion (Arcofac) for 4 weeks. During the therapy the patients' weights remained essentially constant.

### Results and Discussion

Feeding of the safflower oil emulsion containing linoleic acid glyceride and pyridoxine hydrochloride resulted in a substantial decrease in serum cholesterol concentration in nine of the ten patients on a general diet. The serum cholesterol concentration of the tenth patient remained constant throughout the experiment. These results are tabulated in Table I. When the study was repeated this drop in serum cholesterol concentration was confirmed in four of five patients. These results are listed in Table II. The results of this investigation on patients receiving normal institutional diets confirms the previous studies on the well controlled but less applicable synthetic diets and it would appear that the use of this emulsion is a realistic approach to an effective therapy for hypercholesteremic patients on such diets.

TABLE I

*Effects of Essential Fatty Acids and Pyridoxine on Serum Cholesterol Levels*

| Patient | Baseline mg. % | After 14 days of Therapy mg. % | After 28 days of Therapy mg. % | 60 days Post-therapy mg. % |
|---|---|---|---|---|
| N.L.[1] | 241 | 208 | 188 | 206 |
| F.W.[1] | 192 | 194 | 162 | — |
| L.G.[1] | 212 | 177 | 180 | 210 |
| M.F.[1] | 278 | 240 | 224 | 240 |
| A.W.[1] | 248 | 202 | 188 | 218 |
| S.P.[2] | 286 | 246 | 242 | 248 |
| M.V.[2] | 247 | 202 | 180 | 218 |
| L.M.[2] | 220 | 222 | 216 | 210 |
| B.E.[2] | 306 | 218 | 200 | 224 |
| H.D.[2] | 293 | 232 | 234 | 243 |

1. 4 oz. of 40% emulsion per day.
2. 8 oz. of 40% emulsion per day.

TABLE II

*Effects of Essential Fatty Acids and Pyridoxine on Serum Cholesterol Levels: Confirmatory Study*

| Patient | Baseline mg. % | After 4 wks. of Therapy mg. % | 4 weeks Post-therapy mg. % |
|---|---|---|---|
| A.W.[1] | 244 | 194 | 244 |
| B.E.[1] | 248 | 225 | 220 |
| N.L.[1] | 234 | 234 | 224 |
| M.V.[1] | 244 | 218 | 240 |
| L.G.[1] | 206 | 184 | 192 |

1. 5 oz. of 65% emulsion (Arcofac) per day.

### Summary

An emulsion containing pyridoxine and linoleic acid glyceride was administered postprandially in an oral dosage to ten mentally ill patients on a normal institutional diet. This medication resulted in a substantial decrease in serum cholesterol concentration in nine of the ten patients. A confirmatory study resulted in a decrease of serum cholesterol levels in four out of five of these patients. It appears that the administration of this emulsion to patients on such a diet is an effective therapy for hypercholesteremia.

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# Schizophrenia as a World Problem

JAMES L. McCARTNEY, M.D.

Schizophrenia has become an increasingly important public health problem and the evolution of the social system appears to be an important etiological factor. The greater the social changes, and the rapidity of these changes seem to correlate with the increase in schizophrenia. Contemporary civilized humanity is tormented by competition, anxiety, doubt, guilt, insecurity, and false standards. The spirit of nationalism leads to group schizophrenia and world-wide tension. To live almost anywhere in the world today means to fight for personal and collective benefits. There is not only sibling rivalry, but racial rivalry, and national rivalry. Anxiety for want of security, anxiety for raw materials to supply the factories, anxiety for food to feed the starving, anxiety that there may be no work, and anxiety over rejection. The history of civilization is based on this natural struggle for survival, but in this struggle the individual is often lost, and he retreats into social isolation.

From East to West, from the Pacific Islands, China, Japan, Ceylon, and India, to Egypt, Italy, France, Germany, England, Russia, and America, mankind has been driven by inner psychological and sociological impulses to win in the unending battle of progress and civilization. This driving energy originates from the egotism of the individual and so the egotism of the nation. If the individual cannot go forward then he is apt to retreat into unreality. Pent-up aggression must express itself or it splits the personality. Indeed, mankind has not existed for more than thirty years without war, and the unresolved aggression has turned to technics of destruction.

### The Marshall Islands

In the Pacific Ocean, almost on the equator, was a group of isolated islands, hardly touched by civilization, known as the Marshalls. Here were ten thousand people without a care in the world, without insecurity, and without sexual guilt, until World War II brought conflict to these shores. Since then has come civilization, marriage vows, and atomic bombs. Before the white man came, there was free love, no need to work, and no schizophrenia, but now these peoples have lost their paradise and many must retreat into unreality.

### Philippine Islands

The Philippine Islands have a population well indoctrinated for many years with the superstitions of the West and then taken under the paternal wing of a benevolent nation. Before national security could be obtained, a disrupting war came, and then these peoples were cut adrift before political maturity. The universities are turning out more graduates than can be absorbed by industry. Schizophrenia is a tragic problem in the young nation, although the authorities will not give a figure as to the incidence of this disease, but it is evident that the psychiatric facilities are taxed beyond limits. Seventy per cent of the population is Roman Catholic, and the dogmas of this religion are confused by the traditions of the pre-Christian bushman.

### Japan

In Japan the individual's status in the family, as well as in society, is determined at birth. The personality is educated and trained from early childhood to adjust to the prescribed way of life in an authoritarian atmosphere. To the extent that the individual is obedient and faithful to his allotted position and is content with his lot in his family and society, he can have personal security. This is now all being threatened by the post-war reconstruction.

The standards of life are still strictly stratified by class: the kind of clothes and their colors, the size and types of houses, the kind of language, when and how to bow, and, in general, how to behave. Conventional morality and traditional restraints are so stringent that the violation of these unwritten laws subjects one to ridicule, or even to exile from the family or community.

Read before the 2nd International Congress for Psychiatry, Zurich, Switzerland, Sept. 6, 1957.

In the past, the family or "house" was the most important symbol in life. Preservation of the family line and its dignity was regarded as the person's most important duty. Consequently, a wife who could not bear children was sometimes divorced and so dishonored. Members who disgraced the family were often expelled. Loyalty to the "house," and if necessary, sacrifice in the interests of the family, were demanded as a matter of routine. The status of the family was determined by the community. Ordinarily, the first son was the head of the main family and the heir. In place of direct inheritance, the other sons were established as branch houses, with subordinate positions.

Three major religions influenced Japanese ethics and helped in forming the social structure. Confucianism, which teaches benevolence, righteousness, propriety, wisdom, self-control, and sincerity, emphasized obedience to parents. From this came Shintoism, which stressed ancestor worship. Buddhism preaches that one cannot exist without the good will and help of other people and of all things in nature. Therefore, the person must be appropriately grateful for the debt one owes to everyone and everything. The Buddhist must not "sacrifice" anmials for eating except fish. He must be satisfied with a modest and simple life and must not aspire beyond his station in life.

Neither of these religions preaches a doctrine of original sin. Therefore, a sense of guilt is aroused by the violation of religious prohibitions, traditional morality, or the regulations of the family or group. The consequences of guilt are primarily the loss of "face" or deprival of group protection. In this fact lies the great importance of "obligation" to the Japanese people. Failure to observe one's obligation to family or society at large, as well as to individuals, resulted in serious deprivations. Obligation, then, as a system of unwritten law, bound individual to individual, and individual to group in a tight network, without regard for the individual's rights or desires.

The young people feel they have been deceived by their leaders, teachers, and even by their parents. This is particularly true for the twenty-year-olds, who were oriented toward an authoritarian, imperialist, ultra-nationalist ideology before and during the war. They were poured into a warlike mental mold from their primary and secondary school days. Told how to think, feel, and behave, how to live and how to die, they were not rtained to think critically or to behave independently. They were given less general cultural education than the older generation. With the occupation by the Americans, this convenient and rigid frame for their life vanished. They were consequently disoriented and confused. Conventional morality lost much of its authority, and, along with Confucianism, Shintoism, and Buddhism, it has little to offer the confused young people. The impact of Christianity is infinitesimal, except to urge legislation against sexual freedom. Thus causing the confusion to become confounded.

Many young people have lost their conventional hopes and ideals and have not been able to formulate new ones. Some insist that they will never trust authority again, while others are pessimistic or even nihilistic. Some of the young people have thrown restraint aside and resign themselves to pleasure and enjoyment. Relations between the sexes is considerably freer in many areas. Some of these young people are extremely ekotistical and do not care about their family, their society, or even their nation. Some are seeking new philosophies, ideologies, or religions; and Communists are increasing among college and university students. There has been a rash of new "religions," the founders of some of which are obviously paranoid. Others retreat to the psychiatric hospital.

It is not surprising that in one psychiatric hospital 70 per cent of the population was schizophrenic and in another 50 per cent bore this diagnosis. It is further stated that at least one per cent of the general population has schizophrenia.

### China

An editorial in the 1889 China Medical Journal stated "that mental diseases are remarkably infrequent in China," but a survey conducted throughout China in 1926 concluded that there were at least 1,341,600 psychotic persons in that country. At that time 12 per cent of these patients were di-

agnosed as being schizophrenic. A study of 2,513 psychotic patients in Hong Kong during 1955-56 showed 35 per cent had schizophrenia.

The Chinese, like the Japanese, had three major religions until the Communists took over after World War II. These were Confucianism, Taoism, and Buddhism. The great mass of the Chinese people are illiterate and haunted by innumerable superstitions. They see devils; they hear them; they feel them; they are possessed by them, and are tormented by them in every conceivable manner. In Taoism these devils are represented as idols. It is imagined that these spirits make noises like rats, ducks, and other animals; that they cry at night, and call for money and food; that they are seen perched on the roofs, which accounts for the typical roof decorations found on Chinese buildings; that they flit vaguely in and out of open doors and windows; that they are seen as black shadows on the walls, and that they are often said to be very large. Some of the female devils are said to be tiny, and some are headless; they frequent dark corners of the room and get under the bed; they have a tendency to pull the bedding and legs of the unfortunate victim. To a psychiatrist these fabrications sound like the hallucinations of schizophrenia.

For several thousand years the Chinese people had been adjusted to the paternal system, with submission to the Emperor and an unquestioned obedience to the father of the family. During the last decade this whole system has been discarded, and actually, the child has been encouraged to inform on the parent. An unthinkable state of affairs until the Communist regime.

Through the centuries the "father-image" had been a fearful, awe-inspiring, terrifying paternal figure, which was never questioned. During the twentieth century, and especially in the last twenty years, the paternal image, which until 1900 was unassailable and invincible, began to appear in another light. The Chinese people saw how another Asiatic race had twice defeated the white people and had defeated and humiliated their elders without incurring punishment. The events in Manchuria, Malaya, the Philippines, Indonesia, and Korea gave them courage, and so they turned against the white man. The "father-image" was completely defeated, for the God of the white man had no power against them. But a new father-image has taken its place. To some extent the new paternity-figure is easier to accept but the basic need for family solidarity is lost.

For centuries the father had inspired awe in his children, and for the last thirty or forty years this attitude was transferred to the new image. Feelings of hate broke loose and were immediately fixed on the white man who had helped to perpetrate the patriarchal system. Then, in the last ten years the present Communist regime began to turn the children against their fathers. When this happened, all the innate feelings of pent-up hatred and wrath were released, and many a schizophrenic reaction was the result.

The problem in Singapore and Malaya is essentially the same as in Hong Kong, as there is about the same percentage of Chinese in the population. There is much Communistic activity in this area, with many strikes, student riots, and revolts against religious traditions.

### Ceylon

Ceylon was for hundreds of years under foreign domination but the majority of the population has remained Buddhist. In spite of the dictates of this religion, the island has been an easy victim of Communistic propaganda. Nevertheless, the native women are still kept under constant protection, and women's dormitories are surrounded by walls Passions must be repressed. Self-denial is the desired goal. Patients don't discuss their sex lives. Pacifism and meditation is the philosophy of the people. The country has an overabundance of monks, who wander the streets, living on the charity of the people. There are about twice as many males as females in the psychiatric hospitals, and about 40 per cent are schizophrenic.

### India

India, with over 600 different religions, still has a caste system which has bred hate and distrust. There are twice as many men as women in the psychiatric hospitals. Over half of all the patients are under forty years of age. Of the first admissions in four hos-

pitals, the rate of schizophrenics was 39 to 67 per cent, with an average of 56 per cent.

It is not surprising that the peoples of India are xenophobic, apathetic, withdrawn, and fatalistic. They are brought up in a tense and hostile environment. Their shrewdness is spoken of as a virtue, yet it reflects a suspicious, vindictive, immature, schizoid mind.

Terror fills the minds of these people who live in the shadows of past centuries. The native goes through life in the constant grip of fear, afraid of the elements, afraid of the knife that might strike his back in the dark, afraid of the darkness itself, afraid of neighbors, afraid of foreigners whom he does not understand and, therefore, cannot trust, afraid of the jinn who lurks behind the trees and the ghouls who, he has been repeatedly told, are so monstrous that no one can elude them, afraid of himself and of his shadow. Little wonder that in India life is one long ordeal of dread and drudgery, thousands of men drown themselves each year in the so-called holy rivers or withdraw from life to become "holy men." These frequent mass suicides, as well as many other forms of self-abnegation, self-punishment, and self-destruction are symptoms of schizophrenia.

In India the individual fights for reasons much closer to himself than political causes. What he is asking on a national scale is essentially what he wants for his own individual needs. The young Indian who wreaks havoc in the streets is basically directing his defiance and hostility against the restraints of cultural and religious traditions, the sickly mysticism, the sacred superstitions, the autocracy of well-meaning but unenlightened parents and teachers. These forces robbed him of dignity, self-confidence, and freedom to grow.

The common Indian, handicapped by deeply absorbed fears, suspicions, feelings of inferiority, and vindictiveness, does not work with enthusiasm; instead he sits in the corner of his dingy hut or uncomfortable flat, underfed, underclothed, his mind handicapped by the sickness of centuries, weaving elaborate tapestries of fatalistic self-consolation. He clings to the perverted but convenient superstition that his fate is predestined by God.

### Western Nations

It has been evident that schizophrenia is an increasing problem in all Western countries. A study carried out in the United States showed 13.8 per cent in private psychiatric office practice, of which 44.8 per cent were male, and 55.2 per cent were female; 37.1 per cent in a private psychiatric sanitarium, of which 45.2 per cent were male, and 54.5 per cent were female; and 29.1 per cent in the New York State hospitals, of which 49.5 per cent were male, and 50.5 per cent were female.

In Canada the first admission to government hospitals in 1953 showed 24 per cent schizophrenia.

In the United States the average annual rate of first admissions to all public psychiatric hospitals in 1948 was 20.1 per 100,000 population. The annual rate for males was 22.1 and for females 18.0, but the figures in the previous paragraph would indicate that the rate is now higher for women than for men.

A study of nationality groups indicated that for those born in Italy, the standardized rate per 100,000 was 30.4; Germany, 35.7; Ireland, 33.0; England, 25.8; Scandinavian countries, 33.8, while it was only 16.0 for native whites of native parentage. The standardized rate for native-born was 22.2 per 100,000 population; for all foreign-born the rate was 32.8. Natives of native parentage had a rate of 16.9; natives of foreign parentage, 26.4; and natives of mixed parentage, 28.1. In comparing the racial groups, the rates for Negroes was 51.1 per 100,000, while for whites it was 25.7; a ratio of 2 to 1. Also, the rate for city dwellers was in excess of those from the country, in the ratio of 2.1 to 1. The married had the minimum rate, the single the highest rate, with the divorced almost as high as the single.

The Western democracies claim to offer a Christian philosophy, truth, ideological tolerance, the spiritual values of humanism, legality, education on Western technology, and economic assistance to nations menaced by hunger and starvation. Their opponents, on the other hand, detect behind this solemn and complex superstructure the policy of exploitation of man by man, of plutocratic or colonizing greed based on military repres-

sion, of extortion perpetuated by misery, of the cultivation of pauperism and the fetishism of the dollar. Such a policy has resulted in religious and class hatred and in the material and moral dependence of a great majority of workers on a small minority of owners determined to defend their hierarchic, outdated, and unjust privileges which cultivate paranoid schizophrenia.

The Communists in Russia insist they are striving for purity and severity of conduct and for the equality of human beings whatever may be their culture, religion, ethnic origin, or color of skin. They claim this will be reached by the disciplined loyalty of the masses, Pavlovian conditioning, the ennobling mysticism of work, and in accordance with a rational and concrete plan of social action. The democracies, however, point out the cruelty of a tyrannical state control, lack of freedom of thought and action, sectarianism, unavowed nationalism in the pan-Slavic sense, inhuman procedures of police supervision, and the impudent propaganda infiltrating the consciousness of nations for the purpose of undermining spiritual ideals. The Communists claim that such a policy has resulted in a decrease in mental illness and especially of schizophrenic reactions.

Both the Western democracies and the Communists are greatly interested in science. The Western bloc proclaims the increased technical perfection of its scientific research, which is confirmed each day by sensational discoveries. Mental illness will be banished by a chemical balance. At the same time, the Communist bloc proudly boasts that its laborious fervor is inspired by the only authentic modern philosophy of science, known as dialectic materialism. Thus, the common man, the potential schizophrenic, is caught between the contradictions that the Communist is spreading across the world, the implacable "truth" of Marxism, while the Western democratic political leader wants to pierce the iron curtain in order to introduce behind it the Paulst "truth." It is uncertain what the identification will be.

## Conclusions

The melancholic truth brought out by psychiatric history is that schizophrenia is on the increase around the world, and, if something isn't done, the human race is well along the road to disintegration. Poised on the brink of chaos, the human race is morally and ethically bankrupt. Forces are loose which might result in total destruction.

There has been a universal deterioration of personal, social, and political morals. Family discord and divorce, movies, and comic books of crime and gangsterism, magazines, books, radio, and dtelevision stories of murder and pathological behavior, labor disputes, aggressive picketing, and sabotage all reflect a climate of tension and hostility the world around. Everywhere there are symptoms of this basic sickness of contemporary society. Increasing unemployment, subordination of the individual to the industrial and administrative machine, the development of numerous modes of evading the realities of life, along with a compulsive urge toward warmaking, betray the degenerative and regressive trends in our civilization.

The complexities of living in the modern civilized world have become too great for unstable personalities. They are almost beyond human comprehension. The rapid extension of the individual's environment through improved communications and transportation has so overwhelmed the civilized world that nothing more can be done than to grasp frantically at isolated bits of reality in the feverish effort to hold the world together.

## Summary

1. The first admissions to psychiatric hospitals around the world showed in Japan 50 to 70 per cent schizophrenia, China 35 per cent, Ceylon 40 per cent, India 39 to 67 per cent, in the United States 29 to 37 per cent.

2. In the United States the rate for schizophrenic negroes was twice as high as for native born whites.

3. The rate was much higher for persons of foreign-born than of native-born parents.

4. The rate was more than twice as high for city dwellers as for country dwellers.

5. Religious dogmas have created a deep sense of guilt in the peoples and caused many individuals to withdraw from society.

6. The rapid changes in the social system and the destruction of the father-figure has removed security from many persons and driven them into schizophrenia.

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# Brain Tumor Presenting as Convulsive Disorder

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The first symptom of a brain tumor is not infrequently the occurrence of epileptic seizures. This holds true especially for tumors of certain regions of the brain. In a series of 62 patients with temporal lobe tumor, 20 had seizures as the initial symptom.[1] When treating patients with convulsive disorders, therefore, one must be alert to the possibility that a brain tumor is the cause. The index of suspicion rises when the onset of seizures occurs well in adult life, when the neurological examination shows abnormalities or when an electroencephalographic slow wave focus is present, particularly if there is an increase in neurological deficit or in the size of the electroencephalographic focus on subsequent examinations.

These criteria are, however, by no means absolute. Many patients developing seizures in mature life do not have tumors, notably in temporal lobe seizures.[2] Positive neurological signs may be caused by organic lesions other than tumor and sometimes may even be found following seizures where no definite organic abnormality can be established. A slow wave focus in the electroencephalogram does not necessarily indicate neoplasm and even an increase in signs or focus does not always prove the presence of a tumor. One may sometimes be misled in this respect due to the fact that the findings may depend on how soon after an overt seizure the patient has been examined. A recent seizure may produce postictal manifestations that lead to an unwarranted assumption that there is an increase in neurological signs or electroencephalographic slow wave focus.

Using the above criteria, there are also patients in whom one has not suspected tumor and who yet do prove to have tumors. We have encountered this situation in a series of 12 patients, who are the subject of this presentation. In the following discussion, an attempt is made to see whether any definite findings might have led to an earlier diagnosis of brain tumor.

Two representative case histories are presented:

*Patient I. B.B.,* a white male, born in 1921, suffered a head injury in 1940, which rendered him unconscious for half hour. Approximately one year later he developed seizures. Initially these occurred as sudden episodes of blindness associated with a feeling of faintness. Thereafter he had attacks of sudden loss of consciousness without convulsive movements. Since 1943 he had attacks at night consisting of a nightmare followed by a generalized tonic-clonic convulsion, and since 1947 these convulsions also took place occasionally in the day time. He was started on anticonvulsant medication and when first seen in 1955 he had had no major seizures for the past five years, but had minor spells with an average frequency of twice a week. These were preceded by a peculiar feeling in his head or hands, he then would stop talking and exhibit confusion and automatic behavior of which he had no recollection. The neurological examination was normal, there was no family history of seizures. The electroencephalogram showed occasional spikes and occasional 3 to 4 per second activity on the left side of the brain, and in the sleeping record there was an active spike focus sharply limited to the left midtemporal region.

For the next 1½ years the patient was treated with several combinations of anticonvulsant medications, but the seizures continued in a frequency of one to two a week. During this time the electroencephalogram was repeated twice and showed an increasing amount of slow wave activity from the

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left temporal region, still with an occasional left temporal spike during sleep. The neurological examination remained normal.

In 1957 the patient was admitted for elective left temporal lobectomy. A pneumoencephalogram showed shift of the ventricular system to the right with an abnormal collection of air in the region of the left temporal lobe, and connected with the ventricular system. The spinal fluid was under normal pressure, but showed a total protein of 155 mg. per cent. Left-sided arteriography showed displacement of the left middle cerebral artery superiorly and of the left anterior cerebral artery to the right. Surgery disclosed a cystic mass in the left temporal lobe, which was partially removed and diagnosed as a cystic astrocytoma upon microscopic examination.

The patient was followed postoperatively for one year. His seizures decreased in frequency to one a month, and his neurological status continued unchanged. There was no visual field defect.

*Patient II. L.L.,* a white female, born in 1926, started to suffer from minor seizures during her first pregnancy in 1945. In the seizures she had a mental picture of two Dutch dolls dancing down a road in front of her uncle's home. The episode was associated with a peculiar tingling sensation through her body and a feeling of faintness. The seizures disappeared after delivery and she had no further complaints until after the birth of a second child in 1947. She then developed another type of seizure, in which she experienced a sense of unreality associated with an unfamiliar, flat taste and an inability to speak.

When first seen in 1949 the neurological examination was normal, and the electroencephalogram was normal except for rather marked but symmetrical and generalized slowing on hyperventilation. Roentgenograms of the skull showed increased digital markings of the cranial vault. There was no history of seizures in the family. The patient was advised hospitalization for further studies, but refused.

Her spells continued, though with decreased frequency, while on anticonvulsant medication. In 1950 she developed tinnitus in the right ear with some minimal loss of hearing on that side. A repeat electroencephalogram now showed an occasional spike and mild irregularity of the alpha rhythm in the right temporal region. Metrazol injection produced a clinical seizure with multiple spike and slow wave activity over the right side of the brain, predominantly in the right temporal region, on the electroencephalographic tracing.

In November 1950 she was admitted to the hospital, after having developed sudden transient episodes of numbness and tingling on the right side of the face, neck an scalp. She also had been amenorrheic for four months. Neurologic examination now revealed minimal blurring at the nasal margins of the optic discs. The remainder of the examination was within normal limits.

Right-sided arteriography and subsequent ventriculography disclosed a large right frontal mass and upon surgery a large caseous tumor containing a cyst was encountered, presenting on the surface near the orbital ridge. The tumor had replaced most of the right frontal lobe and protruded into the middle fossa, depressing the tip of the right temporal lobe. Complete removal was apparently obtained. Microscopic examination revealed an epidermoid tumor.

The patient was followed for seven years postoperatively. The neurological examination returned to normal and she had no recurrence of seizures. She was able to discontinue all anticonvulsant medication.

## Discussion

In our series of 12 patients, the onset of seizures was recorded at age 13, 15, 18, 18, 20, 20, 23, 28, 31, 33, 33 and 34 years respectively. The time interval from the onset of seizures until a tumor was definitely suspected and proven varied from two to twelve years in 11 cases while in the twelfth case (Case No. I) tumor was diagnosed 16 years after onset of seizures as a surprise finding upon pneumoencephalography prior to elective temporal lobectomy for temporal lobe seizures. The average interval was 6⅓ years.

*Neurological Examinations:* The neurological examination remained within normal limits in eight patients for two to 16 years after onset of seizures (with an average of five years). In one patient there was slight blurring of the optic discs when examined 12 years after onset of seizures, but this had been noted several years previously in another hospital where air studies were reported as showing bilateral cortical atrophy. In one patient, seen four years after onset of seizures, there was a slight increase in reflexes in the left arm, but he had had a normal air study elsewhere. In one patient there was minimal right lower facial weakness when first seen eight months after onset of seizures. Arteriogram and pneumoencephalogram were normal and no other signs developed during a follow up period of 1½ years, after which time the correct diagnosis was established by ventriculogram. In the last patient there was occasional postictal clumsiness of the left hand and increase in left arm reflexes three years after onset of seizures.

*Roentgenographic Contrast Studies:* It is interesting to note that several patients had normal arteriograms and/or air studies, which had led to a false sense of security.

One had normal air studies, one had a normal arteriogram, and one had a normal air study and arteriography, respectively eight months, four years, and seven years after onset of seizures. One patient had air studies seven years after onset of seizures, which were interpreted as showing bilateral cortical atrophy. In one patient ventriculography one year after onset of seizures had shown a questionable minimal shift. Surgical exploration was carried out at that time and a small area of softening was found in one frontal lobe without manifestation of tumor. In another patient a pneumoencephalogram one year after onset of seizures showed a questionable shift of 7 mm. across the midline. There was a slight rotation, however, on the AP films, and as the form of the ventricles was normal, arteriography was performed, which was within normal limits.

*Family History of Seizures and Other Possible Etiologic Clues:* In general there was no family history of seizures in these patients but this was not universally true. One patient had a paternal aunt and a distant family member on the maternal side with seizures and the brother of another patient had suffered from seizures. In one patient seizures started one year after a head accident with loss of consciousness for half an hour, in another seizures started two months after he had been involved in a car accident with head injury, but no loss of consciousness. One patient had suffered from a head injury with prolonged loss of consciousness 16 years prior to onset of seizures. In two patients seizures started in relation to pregnancy, in one eight days after the birth of the third child and in the other during the first pregnancy.

*Electroencephalography:* Electroencephalographic examination also usually failed to give a definite clue regarding the presence of a tumor.[3] As a matter of fact, five patients had normal electroencephalograms (respectively 2, 3, 3, 4 and 12 years after onset of seizures). Four patients showed a focal spike with some associated focal slow wave activity not distinguishable from "scar" foci (respectively 1, 3, 3 and 14 years after onset of seizures). Two patients had a sharp wave focus on the electroencephalogram (½ and 2 years after onset of seizures) and only one had definite focal slow wave activity (4 years after onset of seizures).

In three patients seizures were recorded (one spontaneously and two metrazol-induced) which accurately localized the focus of onset but in other ways were indistinguishable from focal seizures recorded in patients without brain tumor.

Nine patients were followed with repeat electroencephalographic examination. Of the five patients with normal tracings, two were given repeat electroencephalograms. One was still normal two years later and one had developed focal slow and sharp wave activity 5½ years later. Of the four patients with focal spike activity on the electroencephalogram, three had repeat tests. In two there was an increase in focal slow wave activity and a less well defined spike (Fig. 1), and the third remained the same. The two patients with a sharp wave focus had repeat electroencephalograms, one of which had remained about the same 6½ years later. In

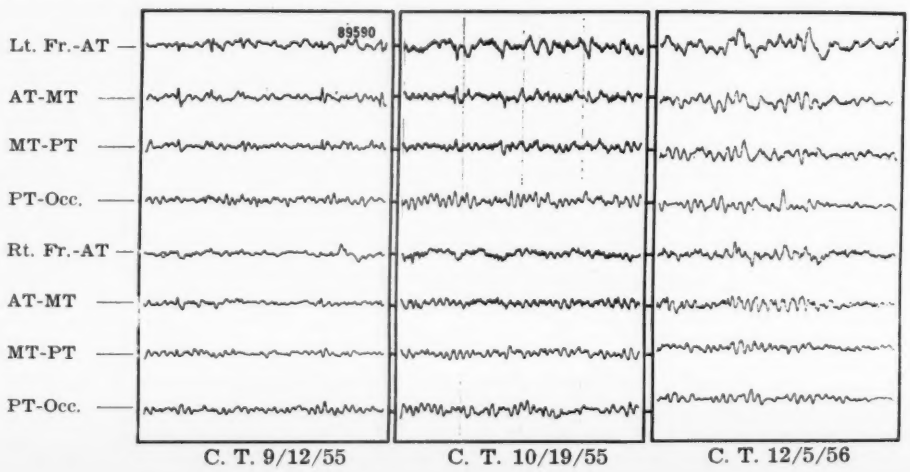


*Figure 1.* The electroencephalogram of this patient initially showed a left anterior temporal spike focus. In the course of the next fifteen months spike activity gradually disappeared and a slow wave focus in the left anterior temporal region appeared instead.

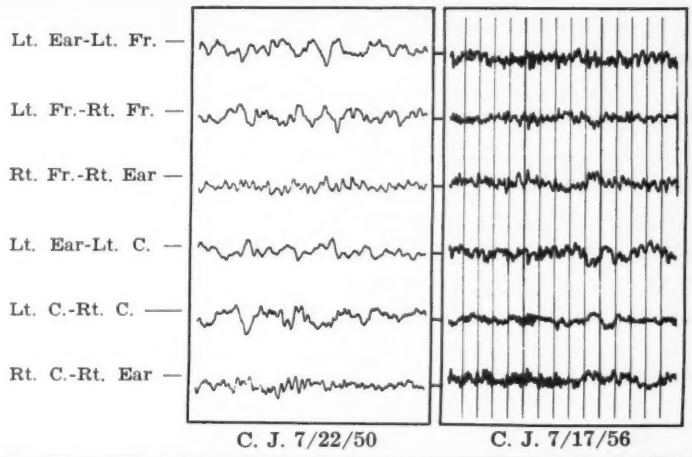


*Figure 2.* Marked increase of focal slow wave activity and spread to adjacent areas in the electroencephalogram upon a repeat examination six years later.

the other the focal abnormality remained the same, but there was increasingly more over-response to hyperventilation in the next year with development of symmetrical and generalized two to three per second slowing. The one patient with focal slow wave activity showed marked increase in slowing and extent of the focus six years later. (Fig. 2.)

*Seizure Types:* The type of seizures was as follows in the different patients: Four patients had focal motor and adversive seizures occasionally followed by grand mal; three patients had psychomotor and grand mal seizures; two suffered from grand mal, psychomotor and focal sensory motor seizures; one had grand mal and motor Jacksonian seizures; one only psychomotor seizures; and one had a definite cortical march starting with focal sensory seizure, progressing to a psychomotor episode which was occasionally followed by facial motor manifestations and finally grand mal.

As such the seizures were not distinguishable from seizures caused by focal pathology of non-neoplastic nature. An interesting phenomenon, however, was that eight patients had a definite change in seizure pattern in the course of their illnesses. This, of course, is seen sometimes in cases without tumors and is due to the influence of anticonvulsant medication or fluctuations intrinsic to the convulsive tendency, but it is rare to observe distinctly different seizure patterns at different times. In this series this phenomenon may well have been related to the growth of the tumor. Examples of this phenomenon can be found in the two case reports presented. To give another example: One patient originally suffered from grand mal seizures during sleep and one month later he developed spells in the day time of a few minutes' duration in which his surroundings seemed strange and the speech of other people did not make sense. This was occasionally followed by a grand mal seizure. One year later other spells occurred in which he experienced a peculiar feeling in his head and then started to run around in circles which finally ended in a fall with unconsciousness but without convulsive movements. Five years after the onset he again developed another type seizure with tingling on the right side of the face and neck followed by confusion. Seven years after onset he still experienced this type of seizure which, however, was now preceded by pain in the right side of the face and accompanied by drawing up of the right arm. Finally he had a typical motor Jacksonian seizure.

*Control of Seizures:* It is also interesting that, though anti-convulsant medication in some instances decreased seizure frequency, not a single patient of this group was ever adequately controlled.

Eight patients have been closely and regularly followed since the onset of their illness and many combinations of anticonvulsant medications were tried. In three patients, seizure frequency was reduced to half the original frequency, in two patients anticonvulsant treatment made no appreciable difference, and in two patients seizures increased in frequency and severity despite medication. One patient was controlled for

ten months, but thereafter seizures recurred and became increasingly frequent, despite increase and change in anticonvulsant medications.

Four patients were seen only at prolonged intervals and the result of treatment was difficult to judge. It seemed that two were somewhat better, one remained about the same and one got worse while on anticonvulsant medicines.

*Pathology:* Finally, we would like to draw attention to the site and nature of the tumors. A preponderance of these tumors were present in the so-called silent areas of the brain—four in the frontal lobe (three on the right side and one on the left), two in the temporal lobe (both on the left), four in the parasagittal regions (two on the left and two on the right). The other two patients were finally operated elsewhere and we do not have adequate data on the surgical and pathologic findings. According to seizure-types and electroencephalographic foci, they probably both had right temporal lobe tumors.

As far as the pathology is concerned, these were in general slow-growing and relatively benign tumors, five being diagnosed as astrocytomas, two as a mixed astrocytoma-oligodendroglioma, one as an oligdendroglioma, one as an epidermoid tumor and one as a meningioma. The nature of the tumors in the two cases operated elsewhere is unknown to us.

## Summary

In treating patients with convulsive disorder, it is often difficult in the early stages to be certain about the presence of brain tumor as the causative agent. However, brain tumor has to be seriously considered when the seizures start in adult life, when the neurological examination shows abnormalities or when an electroencephalographic slow wave focus is present. These findings, however, do not render absolute proof for a diagnosis of brain tumor. In the present article a series of twelve cases with convulsions is presented. These do not meet with all of the above criteria but yet were proved to have brain tumors 2-16 years after the onset of seizures (with an average of 6⅓ years). These patients were studied in an attempt to define other criteria which might raise the index of suspicion as to the presence of brain tumor as a causative agent of the convulsive disorder. It was noted that in general these patients reacted poorly to anticonvulsant medication as regards seizure control. Not a single patient was ever completely controlled and several showed an increase in frequency and severity of seizures despite anticonvulsant medications. It was also interesting to note that a majority had a definite change in seizure pattern during the course of their illness, and occasionally three or four different types of seizures superseded each other. Repeat electroencephalographic examinations were sometimes helpful in that normal electroencephalograms might change subsequently and show focal abnormalities or an initial spike focus be increasingly replaced by focal slow wave activity. In this set of circumstances, then, the clinician should be alert to the possible presence of a brain tumor. However, a study of this group revealed that no clear cut and definite criteria can be established and one always has to keep in mind the possibility of a brain tumor when following a patient with a convulsive disorder, unless another etiology can be definitely established.

A sense of false security may be obtained by repeated normal neurologic examinations, by normal roentgenographic contrast studies and sometimes by clues in the history indicating the occurrence of seizures in the family or the presence of previous head injury. It is also noteworthy that in half of our cases the convulsive disorder started before the age of 21 years.

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# Sleep Treatment in Mental Disorders

## Results of Four Years of Trial

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In a previous communication[1] results of preliminary observations on sleep therapy were reported. The technique involved the use of chlorpromazine and three different time reacting barbiturates. It was found to be useful as a therapeutic and research tool in mental disorders. Since that report several papers have appeared in European and South American literature on the subject,[2-12] emphasizing in particular the role of new phrenotropic substances, but there has not been much in the American literature on this problem. The present paper is a report of a study which has reached its fourth year of trial and proposes to present the results of prolonged sleep treatment and its modifications in mental syndromes. In addition certain theoretical problems will be discussed.

### Material and Method

*1. Subjects:* 114 patients suffering from varieties of mental syndromes underwent prolonged sleep treatment. All but 8 had remained refractory to other kinds of therapy, and the sleep treatment was considered as a last resort. They formed two groups: 1st group consisting of 66 patients who received sleep treatment alone, and the 2nd group consisting of 48 patients who received electric shock while undergong sleep treatment. The reason for the addition of electric shock to sleep was twofold: the refractory nature of patients' disorder, which was mostly either schizophrenia or manic-depressive state, usually with many previous relapses; and the explicit aim of producing a rapid regression and disorganization.

All patients prior to sleep treatment underwent complete biochemical and EEG investigations. The first 25 patients received once weekly liver function tests (cholesterol, serum bilirubin and cephaline cholesterol) and twice weekly alkaline phosphatase determinations. The latter test alone was done twice weekly in the remaining patients because previous studies[14] had demonstrated the relative good prognostic value of this test in hepatic dysfunction during chlorpromazine therapy.[13] Ten patients were tested psychologically (abbpreviated Wechsler, Figure Drawings and Rorschach) before the treatment and 4 months after.

*2. Medication.* The production of a state of sleep as near to normal physiological level as possible, lasting for 20-22 hours a day was partially realized through the administration of 3 different time reacting barbiturates in addition to chlorpromazine or promazine, and occasionally phenergan. The barbiturates consisted of a short acting (Seconal), moderate acting (Nembutal), and a long acting one (sodium amytal or Veronal). With the expectation that a certain plateau of sleep would be produced, chlorpromazine was used in about 50% of the patients, and promazine in about 40%, and those in whom evidence of liver dysfunction developed under chlorpromazine. The purpose of adding these phrenotropic substances was their barbiturate potentiating effect and their demonstrated action on mental disorders.[13,15] Phenergan was used in about 10% of cases mainly as a potentiator of other medications. The basic formula consisted of:

| | |
|---|---|
| Seconal | 100 mgm |
| Nembutal | 100 mgm |
| Sodium amytal | 150 mgm (or Veronal) |
| Chlorpromazine | 50 mgm (or promazine 100 mgm) |

The duration of sleep treatment ranged from 18 to 60 days with an average of 25 days. Experience revealed that 15-20 days of sleep was an optimum time.

*3. Nursing Care and Adjustment of Drug Dosage.* Two situations existed and were as follows: (1) individual sleep treatment, where the patient was treated in a private room; and (2) collective sleep therapy where

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from 4 to 8 patients were treated in one room called sleep room or ward. The staff of the sleep room consisted of 2 psychiatrists, 3 nurses and 2 nurses aides.

The two techniques applied consisted of: (1) a triple waking technique, the patient being awakened three times a day, at 8 a.m., 2 p.m., and 8 p.m.; and (2) a double waking technique: the patient being awakened twice daily, at 8 a.m. and 8 p.m. These methods were used according to the degree of the patient's tolerance, and the smoothness of sleep. Experience showed that the first technique was safer and less stressful. During the waking hour temperature, pulse, blood pressure and respiration were recorded before the patient was moved out of bed to be cleansed, fed and toileted. Then he was encouraged to eat anything he wished, sitting on a chair. Solid food would usually be taken in the first week, and from then on semi-solid foods. The minimum amount of caloric intake was put at 1,500, and the minimum amount of fluid intake at 2,000 ml daily; the latter was modified according to the output. In addition patients received vitamins parenterally. The nursing care between waking periods consisted of changing the position of the patients every two hours and administration of a mixture of oxygen-carbon dioxide if the respiration became shallow. To facilitate the excretory functions milk of magnesia was given routinely every other day, and colonic irrigation if no elimination had occurred in two days. Urine was catheterized if no elimination had occurred within 12 hours. Five units of regular insulin were given half an hour prior to each meal to increase appetite.

The basic medication formula could be adjusted easily in the first few days according to the degree of wakefulness. In order to standardize the situation, the degree of wakefulness was divided into four grades in relation to stimuli which were utilized systematically in the following order: light (opening door, flashing light on patient), sound (non-verbal, verbal); touch, movement (part, and whole body); and pain. According to the responses to these stimuli the following qualitative four grades of wakefulness were adopted:

4—Patient wakes up, opens his eyes, talks freely, moves in and out of bed relatively unaccompanied, and eats alone.

3—Patient wakes up, opens his eyes, talks with difficulty, moves in and out of bed with difficulty, has to be fed and accompanied.

2—Patient wakes up, opens his eyes, talks with difficulty, can move in bed but not out of bed, and has to be fed.

1—Patient wakes up, opens his eyes, mumbles and moves in bed.

*—Patient wakes up, does not open his eyes, does not talk and except for few movements indicating his waking up, does not move.

These grades were used by the nurses and the medications could be adjusted accordingly. Doubling the dose of two barbiturates usually was enough to change the degree of wakefulness about one grade. In cases of restlessness, particularly at night, an intramuscular injection of 50 mgm. chlorpromazine, or 100 mgm. promazine would carry the patient over till the next medication. It should be noted that the amount of medication required, and the smoothness of the sleep was largely dependent upon the willingness of the patient to accept the treatment. For this reason all patients were interviewed at length prior to the treatment, the procedure explained and consent obtained. In some resistant patients it was found that administration of Seconal, 100 mgm. ten minutes prior to intake of the rest of medication, during the meal, was sufficient to provoke a degree of drowsiness and cooperativeness so that other drugs would be taken with little resistance.

In the group of patients who received sleep plus electric shock the latter treatment was administered in the morning during the first nursing period, before the first meal, in routine manner with little or no additional sedation. The rate of administration was usually three times a week, except in those for whom a rapid regression was planned. In these cases electric shock was administered daily.

*4. Criteria of Improvement.* These consisted of 4 items: Adaptation to ward; subjective comfort; ability to go home; ability to resume work. The patient was categorized as slightly, moderately, or markedly improved, according to whether he has shown an increase in 2, 3 or 4 criteria.

**Results**

*A. Short Term.*

The following two tables give the overall results of the sleep treatment alone and with electric shock, within 2-4 months after the cessation of treatment. The long term follow up results will be discussed separately.

*1. Sleep Treatment Alone.* This group consisted of 23 schizophrenic, 14 manic-depressive, and 29 neurotic patients.

Of 23 mostly recurrent schizophrenics, 4 showed marked improvement, and 12 moderate improvement according to the criteria described above. In 2 cases where complete psychological tests were repeated 4 months after the patients' discharge from the hospital, the underlying schizophrenic structure appeared unchanged. The existent alterations were an increase in the strength of some defenses. Our previous impression about the better responsivity of cases with preponderance of affective symptomatology[1] was relatively corroborated in the present series. The observation is in correspondence with Russian authors' opinion.[16]

Of 14 manic-depressive patients' 6 showed marked and 4 moderate improvement. The manic or agitated patients were the most responsive. It should be noted that these patients were those who could not be managed with chlorpromazine or promazine alone. Two agitated depressed patients who responded well to sleep, relapsed a few days after and had to be put on electric shock therapy. This experience led us to combine electric shock with sleep in manic or agitated patients, who showed the return of symptoms when the level of sleep was lightened after the second week of therapy. In several cases manic-depressive cycles could be observed while patients were in sleep. The appearance of a depressive state in an initially manic patient was taken as an indication for the addition of electric shock therapy.

Of 29 neurotics, the favorable response was observed mainly among mixed psychoneuroses (4 marked and 4 moderate improvement), and anxiety hysterias (2 marked and 1 moderate improvement). The majority of these patients developed marked feelings and behavior of dependency after the sleep, most of whom responded to supportive psychotherapy, and one could resume his psychoanalysis.

*2. Sleep Treatment With Electric Shock.* There were 49 patients in this group. They had received almost all other forms of treatment, a majority of them were recurrent cases, and their prognosis was judged poor at the onset.

Of 15 schizophrenics, one showed marked and 6 moderate improvement, mainly in form of better home and social adjustment, the schizophrenic structure remaining unchanged. All these patients depended for the maintenance of their improvement on the follow-up psychotherapy.

Of 16 manic-depressive patients, 7 showed marked and 7 moderate improvement. It was evident that this group formed the major indication of combined sleep and electric shock therapy.

Of 18 neurotic states, 16 of whom were mixed psychoneuroses, only 5 showed moderate improvement. As expected character neuroses did not respond.

It should be noted that in combined electric shock and sleep considerable confusion will set in quite early—much earlier than with electric shock alone—and will last until about 3 weeks after the cessation of treatment.

*B. Long Term Follow-Up*

In both groups, particularly group 1 (sleep alone) the immediate outcome of therapy and its maintenance in the post-hospitalization period (1-4 months) appeared to be related to (1) pre-sleep therapeutic formulation; (2) the appearance of deep regression during the sleep; and (3) post-sleep rehabilitation program.

If no therapeutic formulation was attempted prior to sleep, and the patient was put, or dumped into the sleep because of the hopelessness of the situation and the despair of the therapist, the outcome in most cases was unsatisfactory. This was related closely to the fact that for such patients no post-sleep rehabilitation program would be devised. In this connection the important problem appeared to be the integration of dependency and emergent regressive needs

into a psychotherapeutically meaningful program.

Out of 38 markedly to moderately improved cases in the sleep alone group, 13 patients could be followed from 2 to 4 years, and 8 from 1 to 2 years (Table III). Of these, 3 neurotic patients have remained well after 4 years, two of whom have been receiving infrequent supportive psychotherapy. One anxiety hysteric is well after 2 years; one after one year. Six patients relapsed after one year, and one patient showed gradually increasing improvement.

One schizophrenic patient remained symptom free for 3 years, with no therapeutic contact except follow up letters. She relapsed after a very stressful social situation, and again responded to sleep and has remained well for about a year. Three other schizophrenics have maintained their social recovery after 2 years; 2 relapsed after one year; and one has shown increasing improvement and remained well for one year.

Of 3 manic-depressive patients, one has remained well for one year, and 2 others have relapsed within a year.

Out of 25 markedly to moderately improved patients in sleep plus EST group, 14 could be followed for a period of one year (Table III). Of these, one mixed psychoneurosis has shown increasing improvement; 5 manic-depressives have maintained their im-

TABLE I

*Results of Sleep Treatment*

| *Diagnosis* | No. of Cases | IMPROVEMENT Marked | Moderate | Slight | Nil |
|---|---|---|---|---|---|
| 1. Schizophrenic | | | | | |
| Paranoid | 16 | 3 | 7 | | 6 |
| Acute Agitated | 2 | 1 | 1 | | |
| Hebephrenic | 5 | | | | 1 |
| | 23 | | | | |
| 2. Manic Depressive | | | | | |
| Depressive, Agitated | 7 | 4 | 2 | | 1 |
| Non-agitated | 4 | 1 | 1 | 1 | 1 |
| Manic | 3 | 1 | 1 | 1 | |
| | 14 | | | | |
| 3. Neurotic States | | | | | |
| Obsessive-compulsive | 7 | | 1 | 1 | 5 |
| Mixed | 15 | 4 | 4 | 2 | 5 |
| Hysteria | 3 | 1 | 1 | | 1 |
| Anxiety | 1 | 1 | | | |
| Character | 2 | | | | 2 |
| Torticolis | 1 | | | | 1 |
| | 29 | | | | |
| TOTAL | 66 | 16 | 22 | 5 | 23 |

TABLE II

*Results of Combined Sleep and EST Treatment*

| *Diagnosis* | No. of Cases | IMPROVEMENT Marked | Moderate | Slight | Nil |
|---|---|---|---|---|---|
| 1. Schizophrenic States | | | | | |
| Paranoid | 8 | 1 | 4 | | 3 |
| Acute Agitated | 2 | | 2 | | |
| Hebephrenic | 5 | | | 2 | 3 |
| | 15 | | | | |
| 2. Manic Depressive States | | | | | |
| Depressive | 8 | 3 | 4 | 1 | |
| Agitated | 5 | 1 | 2 | 2 | |
| Manic | 3 | 2 | 1 | | |
| | 16 | | | | |
| 3. Neurotic States | | | | | |
| Mixed | 16 | | 5 | 4 | 7 |
| Character | 2 | | | | 2 |
| | 18 | | | | |
| TOTAL | 49 | 7 | 18 | 9 | 15 |

TABLE III

*Long Term Follow Up Results*

| *Diagnosis* | No. of Cases | Years of Follow-up | IMPROVEMENT |
|---|---|---|---|
| SCHIZOPHRENIC STATES | | | |
| Sleep alone | 1 | 4 | Relapse after 3 years |
| | 2 | 2 | Continues |
| | 2 | 2 | Relapse after 1 year |
| | 1 | 1 | Continues, increasing |
| Sleep with EST | 3 | 1 | Continues |
| | 3 | 1 | Relapse after 1 year |
| MANIC DEPRESSIVE STATES | | | |
| Sleep alone | 1 | 1 | Continues |
| | 2 | 1 | Relapse after 1 year |
| Sleep with EST | 5 | 1 | Continues |
| | 2 | 1 | Relapse after 1 year |
| NEUROTIC STATES | | | |
| Sleep alone | 3 | 4 | Continues |
| | 1 | 2 | Continues |
| | 1 | 1 | Continues |
| | 1 | 1 | Continues, increasing |
| | 6 | 1 | Relapse after 1 year |
| Sleep with EST | 1 | 1 | Continues, increasing |
| TOTAL | 35 | | |

provement, and 2 have relapsed; 3 schizophrenics have maintained their recovery, and 3 have relapsed.

**Modification of Sleep Treatment**

Certain modifications of sleep treatment appeared necessary due to the fact that the results of the therapy were, on many occasions, either unpredictable or inadequate. Although many patients in sleep alone showed considerable recovery, the course in others indicated that regression had a certain positive relationship to the outcome. It seemed that those cases who regressed to anal and oral levels of behavior and experience showed a greater tendency to progression. Theoretical aspects of this problem will be discussed later. This observation and the previous studies on the area of regression-progression (disorganization-reorganization)[17,18] led to the conclusion that perhaps fostering the regression, already in action during sleep, psychotherapeutically or by other means would be useful. Hence two methods of inducing deeper regression were envisaged: anaclitic therapy and EST disorganization.

*1. Anaclitic Therapy Induced by Drugs.* A detailed account of this procedure was reported elsewhere.[19] Briefly it consists in keeping the patient in a prolonged light sleep, by using higher doses of chlorpromazine or promazine and lower doses of barbiturates, and allowing him to regress through production of a state of relatively complete dependence, similar to or symbolically perceivable as the mother-child situation. This was realized by intensive thrice daily interviews, averaging 1%-2 hours each, with the therapist engaging the patient in intensive psychotherapy, while feeding him. Emphasis was placed upon free association, analysis of dreams and phantasies. During absence of the therapist a nurse was present in the room at all times, providing the needs of the patient.

Due to the great amount of time and effort involved in the anaclitic setting, only 4 cases have been treated in this way: 2 neurotic anxiety states, one phobic case, and one psychotic depression. Except for one anxiety neurotic the other three patients showed marked improvement. The failure in the one unimproved case could be attributed to the resistance to regression. This patient who was seen one hour twice a day, and spoon fed only once a day, did not show signs of deep regression, e.g. incontinence, confusion, and remained awake most of the time. He had a male attendant.

*2. Regression Produced by Combined EST and Sleep.* This was discussed in main outline in the previous sections.

*3. Sleep Group Therapy.* This was carried out in order to decrease the amount of nursing care. To increase the efficiency a sleep ward was set up where 4 to 8 patients could be treated simultaneously. The innovation introduced into this setting was what could be called sleep group therapy. For this purpose during the morning waking period all patients were gathered around one dining table, and while eating, were encouraged to verbalize their problems, and speak particularly about their experiences during the sleep. The great difficulty for such a setting was the initiation of a group feeling and group formation, mainly due to the differences in waking states of patients. Although our experience has been limited and fragmentary in this regard, the immediate usefulness of such a group seems to be the supportive role which it may have in decreasing anxieties about sleep and thus a decrease in the amount of medication and an increase in the smoothness of the procedure.

**Complications**

In general, complications were minimal and amenable to correction without lengthy interruption of sleep. They consisted of sudden rise in temperature to 103-104°, and then a sudden fall to normal limits within 12 hours in 4% of patients; maculo-popular rash in 7% of cases; Parkinson-like syndrome in 5% of the chlorpromazine patients treated but none in the promazine cases; a mild peripheral radial paralysis of the left hand in one case which disappeared within a month. Four cases developed bronchopneumonia between the first and the third week, for which the sleep was discontinued for about 5 days to allow the recovery under antibiotics, and resumed again with maintenance doses of antibiotics. Three cases developed post-sleep convulsive seizures, one of

whom was a known epileptic. Alterations of liver function tests in form of rise in alkaline phosphatase appeared in 24% of cases treated with chlorpromazine. The sleep was continued while chlorpromazine was changed to promazine with no difficulty.

### Indications for Sleep Treatment

As yet a definitive series of indications cannot be outlined for sleep treatment. In our experience this was due, at least in part, to the nature of patients treated, the majority of them being refractory and apparently hopeless cases. Some Russian and French authors[20,21] etc. give psychosomatic and neurotic disorders as the major indications of sleep treatment. Having treated no psychosomatic cases, we cannot pass an opinion on this aspect. In schizophrenic states Ey's results have been unsatisfactory,[12] while Clapp and Loomis and Smolenski (cited by Wortis) found better results.

From present observations the major indications for sleep treatment can tentatively be given as follows: manic states, agitated depressions, acute schizophrenic states, agitated paranoid states, mixed psychoneuroses and anxiety hysterias. In the psychotic states mentioned sleep treatment should be instituted after a failure with phrenotropic substances. In mixed psychoneuroses and anxiety hysterias the treatment of choice seems to be anaclitic therapy by a modified form of sleep therapy as described. It is possible that to produce definitive changes in personality structure the anaclitic setting is the situation of choice in the majority of cases, psychotics or neurotics. However, further studies are necessary to bear out the validity of such an assumption.

### Discussion and Theoretical Considerations

Until now theoretical considerations about sleep treatment have been mainly physiological,[23-26] some of which were discussed in a previous report.[1] They seem to be based mainly upon the hypothesis of psychosomatic restitution, cortico-subcortical rearrangement or rest. This conception is not very different from what Celsus de Medicina had proposed in antiquity.[36] Pavlovian concept of "protective inhibition" of the cortex during sleep and subsequent restitution of cortico-subcortical connections, which is the basis for utilization of sleep treatment as the major form of therapy of mental disorders in Russia, has similar implications.

It is evident that like all matters pertaining to the mind, physiological considerations alone are inadequate to explain sequences of existential events, and they form only one chain in the sequence of "physiological process-total organism-psychological process."[27] What we have observed in sleep treatment indicates that sleep as such is not always beneficial; that the psychological restitution occurs unpredictably in many cases; that the patient's experiences during the sleep are of paramount importance, this in particular in relation to the depth of regression. However, psychological hypotheses alone seem to be inadequate for the explanation of the events during the sleep treatment. Psychological considerations form only one chain in the sequence of "psychological process-total organism-physiological process." Psychological theories of sleep under the gradual emphasis that Freud put upon the ego have been considering the defensive role of sleep.[28,29,30] It is apparent, however, that in sleep disturbances the problem resides in conflicts within different psychic agencies in function, while here, in prolonged sleep, the state of sleep is pharmacologically induced and is enforced upon the organism beyond and in spite of internal conflicts; the organism has no choice. This and the observation that regression during the sleep and an apparent increase in ego strength after the sleep were the sole variables which were seen in improved cases seem to lead to certain inferences making possible the assumption that the therapeutic value of prolonged sleep was due to two interrelated phenomena conceptualized as: (1) a split in ego system; and (2) a regression beyond the fixation positions resulting in a rebound process of reorganization. It should be emphasized that the following inferences are taken to be useful especially in patients who received sleep alone.

Due to the imposition of sleep on the organism by pharmacological means, it is necessary to take as a starting point for explanation the first sequence of "physiological process-total organism-psychological

process," and end with the last sequence. The role of central reticular activating system in the states of wakefulness, arousal and sleep has been generally accepted. It is consistent, then, to begin the inferences at this level. It appears that the activity of this system is responsible for what can be called "attentive prehension" of the internal and external events.[31] Put otherwise, it can be said that through the diffuse influence of this system the organism is placed in a state of effective or active "presence in the world".[31] Kubie[32] and Azima, et al.[31] have postulated that to comprehend the psychophysiology of certain mental events it is conceivable to maintain that some functional neuronal systems are concomitant and underlie some unconscious processes, and may be represented theoretically as composed of some self-sustaining, self-repetitive, self-energizing neuronal sets beyond the active phase of other neuronal patterns. It appears logically consistent to maintain that the establishment of a relationship between these self-sustaining systems and the non-specific reticular system puts the organism in a state of attentive and effective prehension of the events represented subliminally before, and provokes what can be designated as emergence of unconscious processes into consciousness, and integration with other functional neuronal sets. This coming into relationship which is compresent with the release of unconscious neuronal equivalents into conscious neuronal equivalents seems, logically, comprehensible as the process of regression. The evidence for regression was apparent in almost all cases within 2 weeks from the onset of sleep treatment (verbally and behaviorally). However, in 12 cases this regression was massive, characterized by the release of anal and oral tendencies, e.g. one patient who was on anaclitic therapy was experiencing a hallucinatory existence full of breasts and milk. It is felt that regression as such cannot explain the recovery, and certain additional conceptualizations are necessary for this purpose. Two such conceptualizations may be given: (1) It was said at the beginning that pharmacologically produced sleep is imposed upon the organism beyond and in spite of its internal conflicts. If we consider what we said about the relation of reticular system to unconscious and conscious processes, and if, in addition, we consider that voluntary effort is necessary for normal sleep, and that the ego interferes in induction and maintenance of sleep, it follows that in pharmacologically induced sleep we are dispensing with the services of the ego, and we are not allowing the organism to utilize the available energy of this aspect of the psyche. We are producing a state of sleep where the ego is more or less not involved, its defenses are not used, and its substantial structure is inhibited and put at rest for a while. This relative inactivation of the ego system may help to explain why the release of unconscious impulses do not lead to psychoses in awakening, but to a relative ego strength, hence some underlying conflicts have been reorganized and abreacted and no longer necessitate the maintenance of some pathological defenses. Post-sleep psychological tests seemed to confirm this assumption in some cases.

This hypothesis can be termed the ego-splitting action of sleep treatment. (2) The other related hypothesis is that a planned disorganization may lead to a rebound process of reorganization. It is felt that in psychopathological states if a temporary regression in some aspects of body scheme (in Scott's sense of the term[33]) can be induced beyond the psychobiological positions where the organism had been initially frustrated and subsequently fixated, and if a reparation and a gratification of these frustrations can be instituted, the fixation positions may be abandoned and an ego-reorganization and progression may ensue. This hypothesis was found to be useful in previous experiments on the problem of isolation and schizophrenias.[17,18] In the present situation it is felt that pharmacologically induced sleep facilitates regression, and if gratification of basic needs can be realized in a psychotherapeutically meaningful fashion, then there may be a great possibility of a progression movement. It was for this reason, perhaps, that patients treated anaclitically showed greater and more stable improvement.

Evidently there are many objections and inadequacies to the above conceptualizations; however, they may be useful in rendering comprehensible some aspects of pro-

longed sleep treatment and the need for further study in this area.

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*Author's Note:* Chlorpromazine (Largactil) and Promazine (Sparine) used in this study were kindly supplied by Poulenc of Canada and John Wyeth & Bros. respectively.

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# Evaluation of Prochlorperazine and a Prochlorperazine-Chlorpromazine Combination in Disturbed Patients

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In studies carried out on psychotic patients, Goldman and Freyhan[1-3] noted a positive correlation between the clinical efficacy of potent neuroleptic drugs and their tendency to produce extrapyramidal signs. Especially with certain phenothiazine derivatives, extrapyramidal signs apparently often herald the onset of clinical changes.

Laboratory tests have shown that prochlorperazine is more potent than chlorpromazine in blocking the conditioned escape response in rats,[4] an index of clinical neuroleptic potency. Clinical evaluations, bearing out these laboratory findings, have shown that prochlorperazine is an effective neuroleptic agent but is more apt than chlorpromazine to produce extrapyramidal signs.[5] These reports encourage us to select prochlorperazine for a clinical trial at the Rusk State Hospital.

## Method

Acutely and chronically disturbed patients were selected for this study. In addition to 67 psychotic criminal patients (with diagnoses of schizophrenic reaction, manic-depressive psychosis, chronic brain syndrome, involutional psychotic reaction, and mental deficiency with psychotic reaction) committed to the maximum security unit, there were from other wards 98 schizophrenic patients —some actively delusional and hallucinatory —and 32 patients with other psychoses, psychoneuroses, or personality disorders. Most of the psychotic patients were hyperactive and assaultive, confused, denudative, and difficult to manage. Other patients had somatic complaints and were chronically tense and uneasy. All patients had failed to attain or maintain appreciable improvement under one or more courses of intensive treatment with insulin or electroshock, sedatives, and various neuroleptic agents. In the study were about equal numbers of men and women, ranging in age from 17 to 65 years, whose illnesses had been present for a few months to more than 15 years.

Except for those on the maximum security unit, patients generally were first given prochlorperazine in tablet doses of 10 to 25 mg. after meals, and the dosage was increased until control was established or side effects intervened. The total daily dosage for the psychotic and psychoneurotic patients during the intensive treatment period was usually 75 mg., although initial dosages ranged from 5 to 100 mg. three times daily. When adequate control had been established, the dosage was maintained for two to six weeks at the maximum effective level and then was reduced to a daily maintenance level about one-third of that given during the initial period of intensive treatment. The usual maintenance dose was one 30 mg. sustained release (Spansule) capsule administered after breakfast.

Because they were extremely difficult to manage, patients on the maximum security unit had been treated previously with exceptionally high doses of either chlorpromazine (up to 2000 mg. daily) or prochlorperazine (up to 400 mg. daily). At these doses side effects, severe drowsiness with chlorpromazine and extrapyramidal symptoms with prochlorperazine, were incapacitating for most patients. In an attempt to obtain maximum control with a minimum of side effects, these patients were given combined, but smaller doses of each of the drugs during the present study. Although there was some variation in the total daily dose, the most frequently employed daily dose for these patients consisted of 600 mg. of chlorpromazine and 75 mg. of prochlorperazine. Whenever possible the drugs were administered in sustained release capsules.

Certain highly disturbed patients received initial intramuscular medication (usually, doses of 10 to 20 mg. of prochlorperazine) until they were willing or able to take oral

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medication. Duration of therapy for all patients in this study ranged from 20 to 50 weeks and averaged 30 weeks.

**Results**

Results of treatment were judged in terms of improved clarity of thinking, orientation, coherence, and interest in life and surroundings; decrease in delusional trends and hallucinatory states; and improvement in prospects for rehabilitation and outside employment. Excluding those patients on the maximum security unit, 39 patients (30%) obtained excellent results under treatment with prochlorperazine and showed complete remission of symptoms. Fifty-two patients (40%) obtained good results: partial symptomatic control of aggression, hallucinations, and delusions and decided and lasting, but partial, improvement in prospects for rehabilitation. Twenty patients (15.4%) obtained fair results: partial, but temporary, control of symptoms of aggression and a definite decrease in hallucinatory and delusional trends. Nineteen other patients (14.6%) obtained no significant benefit.

Hyperactive, emotionally disturbed patients seemed to derive the most striking benefits from prochlorperazine therapy, but the drug was also highly effective in controlling symptoms of anxiety and tension in other psychotic patients, as well as in those with psychoneuroses and personality disorders. By starting with fairly high dosages of prochlorperazine and leveling off if the patient developed extrapyramidal symptoms, initial control was established rapidly, and previously assaultive or disoriented patients became calm and cooperative.

Thirty-six patients who had failed to show or maintain appreciable improvement under previous therapy were furloughed from the hospital after treatment with prochlorperazine. If the patients remain on furlough for one year without a return of symptoms they will be discharged permanently from the hospital. Since the completion of the study (almost six months), only eight patients have returned to the hospital for a second course of therapy. Results in these patients were especially gratifying, for they had not responded to other neuroleptic drugs, electro- or insulin shock therapy, or sedatives, and all undoubtedly would have been relegated permanently to long-term custodial care.

There were no serious side effects. About one-third of the patients taking high doses of prochlorperazine developed extrapyramidal symptoms: usually, mask-like facies or rigidity of the arms. No cogwheel rigidity was seen. Symptoms usually disappeared after medication had been discontinued for two to four days and did not recur when the same or a reduced dosage was resumed. The drug was well tolerated and evidently has a wide margin of safety, even when used in high dosages during periods of intensive therapy. Transferring patients from the parenteral to the oral form of prochlorperazine did not alter the efficacy of treatment, and the course progressed unchanged.

After treatment with prochlorperazine the need for electroshock therapy was reduced by at least 96 per cent. Property destruction also decreased markedly, and patients receiving prochlorperazine seldom needed seclusion or restraint. Injuries and fighting rarely occurred and consequently the ward atmosphere was completely changed. Moreover, since the nursing staff were freed from disciplinary functions, they could provide an active social program in which more patients participated productively. As patients became calm and cooperative, psychotherapy was facilitated and they developed better insight into the causes of their illnesses.

Under concomitant therapy with chlorpromazine and prochlorperazine, 17 (25.4%) of the psychotic criminal patients on the maximum security unit obtained excellent results. Thirty (44.8%) obtained good results and 13 (19.4%), fair results. Seven patients (10.4%) obtained no significant improvement. As Barsa[6] reported, combination therapy with chlorpromazine and prochlorperazine proved highly effective in combating delusions and hallucinations of schizophrenic patients. By using combined, but smaller doses of chlorpromazine and prochlorperazine, it was observed that the incidence and severity of side effects that had occurred with these drugs when used singly at much higher doses were greatly decreased. Only three of the 67 patients exhibited extrapyramidal symptoms and none were list-

less or drowsy. The combination therapy was especially useful in this group who, because they are wards of the court and cannot be released, have to be maintained for long periods in the hospital. It was our opinion that the combined neuroleptic therapy aided them in adjusting successfully to work and ward routine.

Ordinarily, too, patients treated with high doses of chlorpromazine could not be permitted to work around trucks or other machinery because of the possibility of hypotensive episodes and serious injuries. The sustained release forms of chlorpromazine and prochlorperazine decreased the incidence of such accidents as falling on stairs or off benches or trucks.

### Comments

The sustained release prochlorperazine capsules are especially useful in providing maintenance therapy for discharged patients. Without peaks and valleys of activity, side effects are minimized. Furthermore, one capsule a day is usually sufficient to maintain therapeutic benefits, thus eliminating the inconvenience—and possible embarrassment—to the patient of multiple dosage regimens.

As long as the daily dosage is maintained at proper levels, the patient can withstand occasional stressful situations that ordinarily might cause a recurrence of disturbed behavior. Most patients who are furloughed from the hospital must be kept on daily maintenance medication and, since the dosage must be adjusted according to the amount of daily stress in the environment, such a patient should be followed by the family physician or in the outpatient clinic.

### Summary

Prochlorperazine was given to 197 acutely and chronically disturbed psychotic and psychoneurotic patients to control delusions, hallucinations, and symptoms of anxiety and aggression. Of these, 67 criminal psychotic patients received prochlorperazine and chlorpromazine concomitantly. One hundred thirty-eight patients (70%) obtained excellent or good results: complete or partial, permanent remission of symptoms. Thirty-three patients obtained temporary symptomatic relief, and 26 failed to benefit from therapy. Thirty-six patients, previously resistant to therapy, were furloughed from the hospital.

At initial high dosages, control of hyperactive, emotionally disturbed patients was established rapidly and enabled them, under psychotherapy, to develop insight into the causes of their illnesses. About one-third of the patients taking high doses developed extrapyramidal signs, which disappeared when medication was discontinued temporarily and did not recur when the drug was resumed.

The concomitant use of chlorpromazine and prochlorperazine in disturbed criminal patients reduce side effects previously seen with higher dosages of each drug without decreasing the efficacy of treatment. Combination therapy with sustained release capsules of both drugs was useful in maintaining prisoners for long periods in the hospital.

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# Narco - Stimulation

ALBERT A. LAVERNE, M.D., and LOUIS J. PADULA, M.D.

"Narco-Stimulation" is a term which has been used to define a chemical non-convulsive therapy in which narcosis and central nervous system stimulation are alternately produced. This new technique is a modification of Meduna's original metrazol convulsive therapy. Its aim is to utilize a convulsive or supra-convulsive dose of an analeptic without the production of convulsions and without the resultant anxiety inherent in conventional metrazol convulsive therapy.

In 1951, one of the authors (A.A.L.) discussed with Dr. L. J. Meduna the possibility and advantages which might ensue if a technique could be developed which would incorporate the chemical action of metrazol in a large dose, and simultaneously avoid the complications of the convulsions as well as the convulsion itself. He encouraged the pursuit of this approach since it was based upon a sound physiological premise. Consequently, experimentation was conducted in the use of convulsive and supra-convulsive doses of metrazol resulting in a technique which was able to successfully antagonize and prevent all convulsive reactions by the use of anesthetic doses of a hypnotic as premedication.

*Technique:*

The patient is administered 1/75th grains atropine intravenously. Then through the same needle, the therapist injects 5 to 15 grains thiopental. When he has determined the optimum level of anesthesia effected, the therapist gives through the same needle 5 to 15 cc. of a 10% metrazol solution rapidly. The patient awakens in from 5 to 30 seconds with no convulsions having been induced, and with little or no apparent anxiety. The vital signs have been relatively unaltered. Six to twenty treatments are required to produce clinical improvement and these may be given daily.

If after six treatments, the patient fails to show significant clinical improvement, this is frequently the result of cumulative treatment anxiety created by cortical excitation of after-discharge phenomena of the analeptic. The therapist should then proceed to administer an anesthetic dose of thiopental immediately following the awakening phase induced by the analeptic for the subsequent treatments. The level to which this anesthesia is carried will depend upon factors such as the individual sensitivity of the patient and the effectivenss eof the antagonistic doses of drugs previously administered. Cortical anesthesia is recommended, and is usually achieved with 4 to 7 grains of thiopental administered in 60 seconds.

The optimum dose of drugs used in any biological therapy may vary among therapists, and from patient to patient. For example, 2 grs. or less of thiopental may produce cortical anesthesia if administered intravenously within one second, whereas, 12 grs. may be required if given slowly over a period of sixty seconds. Obviously, the deeper the anesthesia, the greater the antagonism to the subsequent analeptic. The levels may vary from superficial unconsciousness, to nystagmus, to the absence of lid reflex and the presence of lid lag, to the fixation of the eyeballs which represents the first surgical plane. We have been using the latter two criteria and have achieved this level in 60 seconds.

Similar factors govern the physiological effects produced by the analeptic. An objective sign of a good physiological response is a marked flushing of the face, neck, and chest occurring immediately after the analeptic is administered and lasting for several minutes. This is usually an indication of at least a maximal dose of analeptic and should be considered the most favorable therapeutic dose for that particular patient.

Whatever criteria are used by the therapist to determine the optimum dose of barbiturate and analeptic, the antagonistic drugs must be safely administered in dose and manner so as to produce physiological changes in the central nervous system of initial adequate depression, then profound stimulation, and, finally, relaxation or depression in the recovery phase.

The average optimum therapeutic range of metrazol is ten to twelve cc. of a 10% so-

lution administered through a 20 gauge needle in eight to ten seconds. If this rate of administration is further reduced, for example, to 15 seconds, the intensity of chemical action is significantly diminished and neuro-chemical summation in the central nervous system is rendered negligible and sub-maximal.

Various analeptics such as Megimide, Picrotoxin, etc., may be similarly used. The method is safe and has no significant side effects or contraindications.

The patient is relaxed, shows no mental confusion, offers no resistance to continuation of treatment, and can be treated on an ambulatory basis.

*Rationale:*

The use of the anesthetic thiopental as premedication completely antagonizes and inhibits the convulsive stimulation at the end organ which the subsequent analeptic would ordinarily induce, without, however, preventing the chemical stimulation of the analeptic upon the central nervous system. The exact mechanism of action is unknown. The following hypotheses are postulated:

a. The large amount of analeptic introduced rapidly is the chemical equivalent of a convulsive or supra-convulsive dose in the form of an electrical discharge from all parts of the brain, but without the induction of a convulsion in any form. This supra-convulsive dose is far above the therapeutic dose used in the conventional analeptic convulsive treatment.

b. The thiopental anesthesia depresses all electrical activity in the brain, both normal and abnormal. The subsequent rapid change produced by the analeptic creates a supra-maximal electrical discharge interrupting the feedback mechanisms which may have been responsible for the abnormal electrical impulses influencing the reverberating circuits in the brain.

c. The physiological changes described may produce sustained beneficial circulatory changes in the brain.

d. Stimulation of the pituitary-adrenal stress system is suggested by clinical improvement in the arthritic symptoms of patients.

*Types of Patients:*

Depressions, severe anxiety states, conversion hysterias, character neuroses, schizophrenics, certain types of manic depressives, and obsessive compulsives are suitable cases. Use in the treatment of geriatric patients offers therapeutic promise.

Several patients who were being treated in this series had an associated rheumatoid arthritic condition, moderately to far advanced, with severe pain, swelling, deformities, ankylosis of joints. They had been previously treated unsuccessfully with steroids, and having resigned themselves to a life of progressive incapacitation, became severely depressed and withdrawn. In the early stage of treatment with Narco-Stimulation, they spontaneously reported marked subsidence of pain, reduction of soft tissue swelling, and increased mobility of the joints. They were now able to considerably reduce the daily amount of analgesics formerly required and yet maintain comfort. Clinical progress was also noted in their mental symptoms and was similarly sustained after cessation of treatment.

*Results:*

Of 50 experimental patients who were refractory to previous forms of treatment, a substantial number have shown significant and sustained clinical improvement up to six months follow-up.

Twenty of 32 schizophrenics, or 63% improved. The paranoids and mixed types responded the best. Of these, eight improved sufficiently to be discharged.

Ten of 15 neurotics, or 61% improved. The depressions and anxiety states responded most satisfactorily.

Two out of three behavior disorders improved.

Improvement was defined as the amelioration of the presenting symptoms to such a degree, that the patient was able to resume relative normal functioning in his environment. A consistent early response was cessation of nail biting in ten patients who had indulged in this habit since childhood.

Of 20 control patients treated only with anesthetic thiopental, five, or 20% improved. In this group there were twelve schizoprenics and eight neurotics. Of the improved in the control group, three neurotics and one catatonic schizophrenic improved.

*Remarks:*

The safe administration of a large dose of analeptic on humans effectively and rapidly reverses the deep levels of anesthesia in-

duced by barbiturates. Such application of analeptic can readily find clinical use in barbiturate poisoning whether by design as in suicide, or fortuitously during anesthesia in operating room.

The therapist should be sufficiently experienced in the management of anesthesia as induced by relatively large amounts of a hypnotic. If the psychiatrist is not so familiar, it is recommended that he avail himself of the services of an anesthetist. It is suggested that a good vein be used in order to be able to rapidly reverse the anesthetic state with the analeptic so that anoxia is obviated. The anesthetic and the analeptic are almost completely and rapidly removed from the central nervous system within a few minutes. Thiopental can be replaced by any liquid or inhalant anesthetic provided it is safe, and readily under the control of the therapist.

If the patient unintentionally develops a seizure as a result of summation electrical discharge in the brain, the convulsion is subdued, of short duration, and harmless, and oxygen may be administered. However, convulsions should be avoided. The initial treatments should begin with lower doses of anesthetic and analeptic and gradually increased with subsequent treatments until optimum dosages are achieved. Some patients demonstrate post-treatment abreaction consisting of weeping, restlessness, etc. lasting a few minutes, and such abreaction is frequently therapeutic.

A maximal dose of analeptic produces profound relaxation. A supra-maximal dose produces relaxation followed by mental or cortical excitation or anxiety which is caused by after-discharge effects. These effects are readily controlled by small parenteral doses of barbiturate administered post-treatment. The depressed patient usually requires a supra-maximal dose of analeptic. The agitated or anxious patient requires a maximal or lower dose. A maximal dose is defined as that amount of analeptic required to exactly and completely reverse the depressant action of the anesthetic on the central nervous system. This will vary with the individual tolerance and sensitivity of the patient to the drugs employed, and upon the rate of administration of analeptic.

Twelve per cent of the patients receiving metrazol show side effects of coughing, sneezing, or vomiting after awakening. This is most likely due to vagus irritability or increased sensitivity of the upper respiratory tract to mucous secretion. This can be controlled by (a) increasing atropine pre-medication from two to three cc's intravenously, (b) or giving the patient antihistamine or anti-emetic as premedication, for example Bonamine, (c) or by lowering the head to bed level and rotating the face to the side, (d) finally, if these measures fail, the rate of administration of metrazol can be reduced to 10 to 15 seconds. Megimide has much less of these side effects but appears to be clinically less effective and less profound in its physiological action due to the fact that five to six times the volume of Megimide must be given to produce adequate reversal of the anesthesia than with metrazol. The physiological action of Megimide, therefore, is necessarily slower and less profound.

The administration of two cc's of metrazol intramuscularly one-half hour before treatment has been found to be useful for the following reasons:

a. This sensitizes the nerve cell to the subsequent stimulation by the large amount of analeptic, and produces a more profound physiological action.

b. It maintains adequate respiration while the patient is under deep anesthesia by Thiopental, so that in the event the therapist should lose the vein while switching to the analeptic, anoxia and its complications are obviated.

If Narco-Stimulation alone does not produce sufficient clinical improvement, then it is recommended that the following combinations or modifications be initiated.

1. Combine with the convulsive therapies, i.e. Electroshock, Insulin Shock or Metrazol Therapy. This combination administered as part of the same treatment or alternated on subsequent treatment days renders refractory patients more susceptible to the beneficial action of the convulsive therapy and reduces the required number of treatments necessary to bring about a clinical remission.

2. The high state of neuron excitation that is created by a Narco-Stimulation treatment can be sustained by giving through the same needle at a slower rate (1 cc. in 3 to 5 seconds) an additional quantity of metrazol or a metrazol-thiopental mixture immediately after the patient has reacted from the previous anesthesia. In this manner, the Central Nervous System excitation is prolonged for 30

to 60 seconds enhancing the therapeutic effect. A mixture of one part Thiopental to three parts Metrazol will maintain the patient in a hypnogogic state and obviate convulsions. If, however, the patient begins to convulse, immediately administer Thiopental to stop the convulsion. It is important to produce physiological sleep in the patient and enhance the recovery phase by terminating the sustained excitation treatment with Thiopental 5 to 8 grs. intravenously in 60 seconds. The total dose of drugs as finally given in this sustained excitation may reach twenty to twenty-five cc's of Metrazol and ¾ to 1½ grams of Thiopental administered over a period of several minutes. This quantity of medication is well tolerated by the patient. However, in the presence of known liver disease, it should be avoided.

*Summary:*

1. The new biological therapy described is a modification of conventional metrazol convulsive treatment, which utilizes the chemical action of a large dose of analeptic upon the central nervous system without producing convulsions in any form and completely avoiding the anxiety that is inherent in the convulsive treatment.

2. Narco-Stimulation introduces a therapeutic medium in psychiatry with a wide range of flexibility. It can effectively be used in combination with other biological therapies.

3. The series is limited in scope and follow-up period. However, the clinical findings thus far observed warrant further investigation, and indicate effectiveness in a variety of psychiatric disorders.

4. The method is safe and has no significant side effects or contraindications.

5. The use of Narco-Stimulation in a medical disease such as rheumatoid arthritis seems worthwhile investigating. It is hoped that its therapeutic possibilities will be further evaluated and explored by workers in this field under more carefully controlled experimental conditions.

*Acknowledgment:* Much of the clinical studies in this report was conducted at Westhill Sanatorium, Riverdale, N. Y.

*Author's Note:* The Megimide used in this study was supplied by Abbott Laboratories, No. Chicago, Ill. The Technique of Narco-Stimulation and the modification described in the report were originated and developed by Dr. Albert A. LaVerne.

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## MEETING OF
# EASTERN PSYCHIATRIC RESEARCH ASSOCIATION, INC.

THURSDAY, JUNE 5, 1958

*Chairman: Leo Alexander*

**Conference on Iproniazid (Marsilid)** 539

SUBJECTS AND PARTICIPANTS:

TOXICOLOGY OF MARSILID

Lowell O. Randall, Robert E. Bagdon (Hoffmann-La Roche, Inc.)

MARSILID TOXICITY

Robert J. Floody, Robert E. Dixon, V. D. Mattia, Jr. (Hoffmann-LaRoche, Inc.)

IPRONIAZID IN PULMONARY TUBERCULOSIS

George G. Ornstein (Sea View Hospital, Staten Island)

IPRONIAZID IN ORTHOPEDICS

David M. Bosworth (Sea View Hospital, Staten Island, N. Y.)

DISCUSSION:

V. D. Mattia, Jr. (Hoffmann-LaRoche), Nathan S. Kline (Rockland State Hospital), Eugene R. Jolly (U.S. Food and Drug Administration), Leo Alexander (Boston, Mass.), Robert E. Bagdon (Hoffmann-LaRoche), Theodore R. Robie (East Orange, N. J.), George Train (Brooklyn, N. Y.), George G. Ornstein (Sea View Hospital), Morton H. Hand (Brooklyn, N. Y.), pital), Charles Buckman (Kings Park State David J. Impastato New York City), Lawrence Gahagan (New York City).

**Suicidal Risk in a Municipal General Hospital** ..... 556

Jacob H. Friedman and Remo Cancellieri (New York City)

**Psychomotor Paroxysms of Non-Epi-Origin** ..... 562

Eugene Revitch (Plainfield, N. J.)

# Introduction

LEO ALEXANDER, M.D.

I think we have all become very much impressed with what Marsilid can do for a patient. I find it indispensable in so-called depressions. I prefer to call these inert psychoasthenic states, a condition which the late Dr. Meyer termed anhedonia. These patients are not responsive to electroshock, they have no self-reproaches and they feel very sorry for thmeselves. They are just inert and inactive. They sleep well in spite of total inactivity. They start becoming sleepless after they have been on Marsilid and don't seem to mind their symptoms. They go to work and enjoy life. This is a rather specific class of cases.

In the classical depressive with intensive self-reproach sleeplessness is the usual symptom. I do not find Marsilid superior to other drugs for such cases. But in the inert states that have not responded to electroshock, Marsilid is uniquely effective.

While drug manufacturers always like to think in terms of an across-the-board, broad spectrum drug, as psychiatrists we are more interested in finding specific action drugs. I think Marsilid is a specific action drug for this condition. Unfortunately it has side effects, which may in rare cases be disastrous. I had a death in a small series of cases, but a colleague treated a much larger series without ill effects. He always made a point of keeping his patients' bowels open by large doses of laxatives and perhaps that may be a preventative. There may be something in the anti-amino oxidase property itself that would render the patient liable to lessened ability to detoxify the effects of various substances.

# Toxicology of Marsilid® and Other Amine Oxidase Inhibitors

LOWELL O. RANDALL, PH.D., D.SC., and ROBERT E. BAGDON, PH.D.

Marsilid® (iproniazid, 1-isonicotinyl-2-isopropyl hydrazine) has been found to be a drug with an unusually board range of activity. Originally introduced as an antitubercular drug, Marsilid has been more recently used in the treatment of angina pectoris and hypertension, acne vulgaris, rheumatoid arthritis and particularly in psychiatric depressive states.[1] Dr. E. A. Zeller, et al., first demonstrated that Marsilid is a potent inhibitor of amine oxidase, an enzyme which has a role in the metabolism of serotonin, norepinepherine and other biological amines thereby preventing their accumulation in the body tissues.[2] Following administration of Marsilid to animals, there occurs an increase in the levels of serotonin and norepinepherine in the brain.[3] These observations indicate that Marsilid mediates its central stimulating activity by altering the metabolism of serotonin, norepinepherine and possibly other biological amines.

The therapeutic significance of Marsilid in clinical medicine has aroused much interest in other inhibitors of amine oxidase which might have a similar activity.

By means of pharmacological experiments in animals, two new drugs, RO 5-0700 (1-picolinyl-2-benzyl hydrazine) and RO 5-0831 [1-benzyl-2-(5-methyl-3-isoxazolylcarbonyl) hydrazine] were found to have even stronger activity than Marsilid. Both agents are several-fold more potent as inhibitors of the amine oxidase activity of isolated rat liver mitochondria *in vitro* and of rat brain *in vivo*. Marsilid, RO 5-0700 and RO 5-0831 can potentiate the central stimulation induced in mice by administration of the precursor of serotonin, 5-hydroxytryptophan, and the precursor of norepinepherine, dihydroxyphenylalanine. In agreement with their higher activity as inhibitors of amine oxidase, RO 5-0700 and RO 5-0831 show evidence of exerting a stronger potentiation of the central excitatory effects of biological amines than Marsilid in mice. However, Marsilid and the benzyl hydrazine analogs produce no stimulation when administered alone to animals.

Reserpine exhibits sedation and ptosis following administration to animals. When mice are premedicated with Marsilid or the newer analogs, the sedation and ptosis induced by subsequent administration of reserpine are blocked. These results suggest that Marsilid, RO 5-0700 and RO 5-0831 probably act indirectly by producing a rise in the brain levels of biological amines which act as the mediators of central stimulation.

Toxicity studies conducted in a number of species indicate that the increase in amine oxidase inhibitory potency of RO 5-0700 and RO 5-0831 is not associated with a concomitant higher toxicity when comparisons with Marsilid are made. The acute toxicity of the three drugs following administration of single dosages is shown in Table I.

TABLE I

ACUTE TOXICITY OF MARSILID, RO 5-0700 AND RO 5-0831

| Route | Marsilid | RO 5-0700 | RO 5-0831 |
|---|---|---|---|
| *Mice—$LD_{50}$ mg/kg* | | | |
| Oral | 950 ± 29 (4) | 448 ± 128 | 193 ± 5 |
| Intraperitoneal | 690 (4) | 187 ± 12 | 190 ± 18 |
| *Rat—$LD_{50}$ mg/kg* | | | |
| Oral | 383 (4) | 240 | 280 |
| *Dog—Single Lethal Dosage mg/kg* | | | |
| Oral | 95 | 95 | >40 |
| *Monkey—Single Lethal Dosage mg/kg* | | | |
| Oral | 640 | 240 | 160 |

The results of measurements of acute toxicity indicate that Marsilid is less toxic than RO 5-0700 and RO 5-0831 to mice and monkeys, while the lethal dosages of the three drugs to rats and dogs are more nearly comparable.

From Department of Pharmacology, Hoffmann-La Roche, Inc., Nutley, New Jersey.

Monkeys weighing 3 kg. tolerated a total oral dosage of 20 mg of RO 5-0700 and RO 5-0831 daily for 14 days without toxic manifestations.

Groups of rabbits were given 5 mg/kg, 10 mg/kg and 15 mg/kg by the subcutaneous route daily for 30 days. At the 15 mg/kg dosage level of RO 5-0700, a moderate lymphopenia and rise in segmented neutrophils was observed. One rabbit receiving this dosage of RO 5-0700 expired on the 27th experimental day. Another rabbit given 10 mg/kg of RO 5-0831 succumbed on the 25th day, but hematological findings among this group of animals remained within normal limits.

Dogs were shown to tolerate 3.5 mg/kg of Marsilid daily for 13 weeks without a reduction in erythrocytes, hemoglobin or hematocrit, while dosages of 7 mg/kg and 14 mg/kg produced a depression in all these values, particularly at the end of one month's treatment.[4] RO 5-0700 and RO 5-0831 were administered to dogs in daily oral dosages of 5 mg/kg for a 30-day period and all these animals remained free of toxic effects.

Chronic toxicity experiments in rats of 13 weeks duration were conducted with Marsilid phosphate, RO 5-0700 and RO 5-0831 employing dosages of 2.5 mg/kg, 5.0 mg/kg and 10 mg/kg. The results obtained in the present study were compared with previous rat chronic toxicity experiments using Marsilid dihydrochloride at dietary dosages equivalent to 5 mg/kg, 20 mg/kg and 80 mg/kg.[4] Some depression in growth was observed with 10 mg/kg of RO 5-0700 and RO 5-0831 and with dosages of 20 mg/kg and 80 mg/kg of Marsilid dihydrochloride. A decrease in erythrocytes, leukocytes, and hemoglobin in rats following administration of Marsilid dihydrochloride was reported previously,[4] but these toxic reactions were not observed in the present study of Marsilid phosphate, RO 5-0700 and RO 5-0831. In all toxicological studies, the dosages employed were considerably higher than the recommended clinical dosages.

The results of this pharmacological investigation indicate that high potency of RO 5-0700 and RO 5-0831 as inhibitors of amine oxidase does not lead to a marked increase in toxicity. This suggests that lower dosages of RO 5-0700 and RO 5-0831 than Marsilid could be employed clinically to achieve a therapeutic response, thereby eliminating some of the undesirable side effects.

*Summary*

1. RO 5-0700 [1-picolinyl-2-benzyl hydrazine] and RO 5-0831 [1-benzyl-2-(5-methyl-3-isoxazolylcarbonyl) hydrazine] are more potent inhibitors of amine oxidase than is Marsilid.

2. RO 5-0700 and RO 5-0831 can potentiate the central stimulation produced by 5-hydroxytyptophan and dihydroxyphenylalanine and this potentiating activity is stronger than that exerted by Marsilid.

3. Toxicity measurements in various species indicate that the higher potency of RO 5-0700 and RO 5-0831 over Marsilid as inhibitors of amine oxidase does not greatly increase the toxicity. Therefore, smaller dosages of the new drugs may achieve a desirable therapeutic response with less side effects when compared with Marsilid.

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# Marsilid Toxicity

## (A Preliminary Report)

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We are presenting only data from studies and reports in the United States. It should be pointed out that our information is far from complete; pressure from heavy research programs, and private practices often prevent many investigators from reporting promptly. In addition, following the recent flurry of lay publicity, we were literally swamped with reports of side effects which had occurred many months previously—some serious and significant, others highly questionable and irrelevant. During this period, for example, we learned of jaundices which had not previously been reported, but we also learned of "Marsilid-induced Asiatic Flu," a "Marsilid-induced dandruff" and an "oriental disease of the esophagus" caused by this drug. We must emphasize, therefore, that the material presented is far from complete, and the statistical aspects are subject to change daily.

Marsilid was distributed to approximately 400 investigators during the period from November 1951 to July 1954. By the end of 1952, data regarding the incidence of side effects occurring during the treatment of some 1,934 patients, had been received through questionnaires from investigators, from manuscripts and published reports, or from correspondence with investigators. In this series, there were reported two cases of jaundice, one of which was a fatality. The physician indicated that the patient developed viral hepatitis and that the death was probably not associated with the administration of Marsilid. Deaths from other causes included one due to convulsions and three to cardio-vascular disorders: one death occurred during an asthmatic attack, another followed an injection of a narcotic and one patient expired soon after an operation.

With respect to the question of jaundice prior to the use of Marsilid as a psychic energizer, reference is made to the paper by Bosworth, et al. (*Quart. Bull. Sea View Hosp.*, 16:134-140, 1955). This report, covering 142 patients, lists four patients with "hepatitis." It should be noted, however, that all had received multiple blood transfusions, and in two the diagnosis of infectious hepatitis was made by a consultant. One patient was subsequently considered to have had an obstructive type of jaundice which was relieved by incision and drainage of a post-hepatic abscess and the fourth recovered while receiving continued therapy with the drug. In three other patients, Marsilid therapy was discontinued because of "evidences of change in liver function," and in one other subject, treatment was interrupted because of "evidence of liver damage (apparently due to infectious hepatitis)."

Estimates based on the quantities of material manufactured and shipped for investigational use and, subsequently, to wholesalers and other types of distributors, indicate that approximately 18,000 patients had been given the drug before its introduction in the psychiatric field.

From early 1957, practically all the investigative work with Marsilid has concerned its application as a psychic energizer. In connection with this program, supplies were made available to 389 investigators. In late 1957, an attempt was made to collect all available data from these investigators through questionnaires; 202 replies were received, covering observations in 3,586 patients. One case of jaundice was reported by each of two investigators. A complete breakdown of side effects, as compiled from these questionnaires, is shown in Table I.

Information on the incidence of side effects during the research program was also obtained by a thorough review of the clinical research files, i.e., files of correspondence with investigators. The distribution of the various side effects which were reported is shown in Table II.

From the Department of Clinical Investigation, Hoffmann-LaRoche, Inc., Nutley 10, New Jersey.

## TABLE I

### Number of Side Effects in 3586 Patients January 1957-April 1958

| | |
|---|---|
| Constipation | 823 |
| Convulsions | 1 |
| Abnormal response to anesthetic and other drugs | 0 |
| Blood changes other than anemia | 5 |
| G-I symptoms other than constipation | 34 |
| Edema | 14 |
| Cardiac enlargement, failure or infarction | 0 |
| Hyperreflexia, clonus or other joint, muscle or tendon changes | 36 |
| Possible metabolic complications | 2 |
| Hypotension | 99 |
| Dry mouth, stomatitis | 11 |
| Impotence or other sexual derangements | 11 |
| Dizziness, lightheadedness, etc. | 64 |
| Rash or other skin reactions | 5 |
| Syncope | 18 |
| Neuritis or other neuropathies, obscure pains | 5 |
| Psychoses and lesser mental changes* | 112 |
| Arrhythmias | 3 |
| Jaundice | 2 |
| Allergic | 1 |
| Weakness | 30 |
| Glycosuria, albuminuria, hematuria, or other abnormal urinary findings | 0 |
| Paresthesias and other abnormal sensory phenomena | 57 |
| Anemia | 1 |
| Abnormal urinary function | 46 |
| Hyperhydrosis | 5 |
| Unclassified | 12 |

*This grouping includes insomnia, irritability, excitability, restlessness, anxiety, etc.

## TABLE II

### Distribution of Side Effects in Correspondence With Investigators

| | |
|---|---|
| Constipation | 21+ |
| Convulsions | 3 |
| Blood changes other than anemia | 1 |
| G-I symptoms, other than constipation | 12 |
| Edema | 17+ |
| Hyperreflexia, clonus or other joint, muscle or tendon changes | 14+ |
| Hypotension | 50+ |
| Psychoses and lesser mental changes | 9+ |
| Allergic | 1 |
| Fatigue | 10 |
| Dizziness | 12 |
| Rash or other skin reactions | 3 |
| Neuritis and other neuropathies, obscure pains | 2+ |
| Hallucinations | 'several' |
| Coma or collapse | 2 |
| Abnormal urinary function | 2+ |
| Impotence and other sexual derangements | 5+ |
| Total | 164+ |

Thus, side effects are reported to have occurred over 164 times. At least 348 patients were involved; the total number was not disclosed by this particular review since some correspondents failed to mention the total number of patients under study.

The question has arisen as to what number of patients has been treated overall. This is of obvious importance if the true incidence of a given side effect is to be ascertained. An analysis of completed questionnaires shows that 3,586 patients were given Marsilid investigationally from early 1957 up to April 1958. Of the questionnaires sent out 187 were not returned. To the total figure should be added a further 1,911 patients listed in reports from investigators but not included in the above questionnaires. Perhaps the most accurate index of the usage of a commercially available drug is the prescription audit. According to these figures for the period April 1957 through February 1958, approximately 350,000 patients received Marsilid in treatment outside of hospitals, while approximately 30,000 patients received the drug in institutions.

After the beginning of 1958, there was a rise in the number of reported cases of jaundice which was coincident with the increased use of the medication. Based on the above figures, it has been estimated that one case of jaundice appears in every four to five thousand patients receiving Marsilid therapy; there is one fatality from this cause in each 16 to 20 thousand patients so treated.

Questionnaires were sent to physicians associated with or reporting cases of jaundice; 76 of the questionnaires have been completed and returned. The information derived therefrom is presented in Table III.

From information received, we have not been able to establish any correlation between age, sex, and dosage on the one hand and the incidence of jaundice on the other. The severity of the jaundice occurring in patients receiving Marsilid at the lower dosage levels remains to be evaluated.

Little time is left for discussion of the far-reaching program which has been established with the cooperation of investigators abroad as well as in many areas of this country, and which seeks to disclose the ultimate pathogenesis of jaundice in patients

## TABLE III

TABULATION OF DATA OBTAINED FROM COMPLETED QUESTIONNAIRES IN 76 PATIENTS WHO DEVELOPED JAUNDICE AFTER RECEIVING MARSILID. FOR COMPARISON, DATA ON THE 13 FATALITIES IN THIS GROUP ARE ALSO INCLUDED.

| QUESTION | | SUMMARY OF DATA | |
|---|---|---|---|
| | | *From 13 Fatalities* | *From 76 Cases of Jaundice* |
| 1. Age (Years) | Range | 29-75 | 21-75 |
| | Average | 53.19 | 49.0 |
| 2. Sex | Male | 2 | 24 |
| | Female | 11 | 52 |
| 3. Total Amount of Marsilid Administered Before Jaundice Appeared | Range | 300-8400 | 62-13,500 |
| | Average | 3957.9 mg | 4656.8 mg |
| 4. Number of Days That Marsilid Was Given Before Jaundice Appeared | Range | 8-120 | 4-213 |
| | Average | 54.3 | 58.0 |
| 5. Initial Daily Dose of Marsilid | Range | 10-150 mg | 10-225 mg |
| | Average | 71.3 mg | 102.2 mg |
| 6. Maintenance Dose of Marsilid | Range | 25-150 mg | 10-300 mg |
| | Average | 69.3 mg | 84.6 mg |
| 7. When Receiving Marsilid Patient Was | in institution | 6 | 15 |
| | treated outside hospital | 7 | 61 |
| 8. Number of Days That Patient Was Jaundiced | Range | 10-40 | 10-103 |
| | Average | 17.8 | 33.9 |
| 9. Patients' Condition Since Disappearance of Jaundice (is patient carrying out same duties as compared to period prior to onset of jaundice?) | yes | | 19 |
| | no | | 26 |
| | unknown | | 18 |
| | died | 13 | 13 |
| 10. History of | | | |
| a) undernutrition | yes | 2 | 12 |
| | no | 8 | 56 |
| | unknown | 3 | 8 |
| b) alcoholism | yes | — | — |
| | no | 11 | 72 |
| | unknown | 2 | 4 |
| c) taking other drugs within previous 12 months | yes | 9 | 60 |
| | no | 3 | 12 |
| | unknown | 1 | 4 |

who develop this symptom during or after a course of treatment with Marsilid. This effort involves much fundamental work in animals, but studies on the clinical level are by no means in the minority. We can do no more than to cite a few examples in each category, in the hope of giving some indication, however inadequate, of the multifaceted nature and broad scope of the endeavor. One study belonging in the first or basic category is designed to determine whether vitamin deficiencies in animals reduce the therapeutic ratio or "safety margin" of Marsilid, or bring to light any specific toxic effects not observed with the compound alone. To what extent and by what mechanism does Marsilid interfere with the metabolism of pyridoxine?—Here is another question to which the answer is being pursued. The principal goal of another animal study is to determine the effect of the acute and chronic administration of Marsilid on the susceptibility of the liver of rats and rabbits to tissue damage by combinations of amines—including 5-hydroxytryptamine, epinephrine and norepinephrine—and by bacterial lipo-polysaccharides or endotoxins. In a similar vein, the possible hepatic toxicity of

Marsilid metabolites is under scrutiny as is the possible interaction of Marsilid and corticosteroids. An especially ambitious project is devoted to detailed metabolic investigations, using $C^{14}$ labeled Marsilid, and another has the objective of learning whether Marsilid can influence the development of hepatitis in chicks. A rather ingenious experiment has been initiated based on the carbon black test for phagocytic function. Marsilid apparently alters the distribution within the liver of carbon black injected into the blood stream. Whether this actually reflects a change in hepatic blood flow remains to be established.

On the clinical side, a variety of studies is in progress. The objective of one of these is to determine the effect of Marsilid upon hepatic excretory patterns, using the technic of external body monitoring of radioactive rose bengal. Workers in three other centers operating independently, are concentrating on the liver profile and striving for answers to important questions—what elements are susceptible to change by Marsilid, what dosages are required, how early can these changes occur, and what is their true prognostic significance—long range as well as immediate? This phase of the program is a broad one and involves not only a careful following of a battery of liver function tests in patients who have developed jaundice, but also periodic testing of liver function in an entire series of patients before therapy and throughout the entire course. One group of 50 patients undergoing treatment for angina has been made available for this purpose as have 100 patients in a psychiatric institution. In still another research center, special attention is being devoted to possible alterations in several varieties of serum transaminase measurements. Thus far, in a small series of subjects presumed free from liver disease, Marsilid has not produced significant changes in any parameter. Finally, all liver biopsy specimens and other histologic material are submitted for review to authorities on liver pathology.

What of liver function changes in patients reported to have become jaundiced in relation to Marsilid therapy? Despite the collection of many data by the questionnaire technic, complete delineation of the pattern has not been accomplished. Most cases, however, have shown a positive cephalin flocculation and elevation of the thymol turbidity and Sgot. Alkaline phosphatase has shown slight to moderate elevation in a large majority. The biochemical picture thus closely resembles that observed in acute infectious hepatitis or in homologous serum jaundice. The same can be said generally for the histopathology of liver tissue from patients who developed jaundice during or after the administration of Marsilid. In fact, in most cases, the histologic picture is described as virtually indistinguishable from that seen in acute viral hepatitis. In this connection, a marked departure from the histology of liver damage from carbon tetrachloride and other common chemicals has been pointed out.

We have been intrigued with the hepatitis problem from several etiologic and research aspects. First of all, we have had reports that Marsilid was associated with jaundice during the period when it was used in the treatment of tuberculosis. However, it does appear that it occurred less frequently and was less severe. We wonder, too, why jaundice associated with Marsilid therapy is rarely observed outside this country. We wonder whether the reported higher incidence of co-existing hepatic disease in mental disorders is not a contributing factor.

Of course, we have speculated on the role of viruses in the development of jaundice during Marsilid therapy. Certainly the incidence, 1 in 4,000 or 5,000 parallels the incidence of viral hepatitis. The pathologic picture is indistinguishable from that observed in viral hepatitis. What is disturbing, however, is that the incidence of fatalities in those who develop jaundice is considerably higher than in the general population group. It is theoretically possible that Marsilid increases the severity of any viral hepatitis much as adrenal steroids do in the presence of bacterial infections.

We are interested, too, in the observations in experiments with carbon black. Does this really reflect a change in hepatic blood flow? If so, we are quite anxious to see if similar findings are observed with other amine oxidase inhibitors under trial, especially those which either do not reduce blood pressure or, in fact, raise it.

# Iproniazid in Pulmonary Tuberculosis

GEORGE G. ORNSTEIN, M.D.

In our experience we have treated 101 patients with iproniazid, dosage 4 mgs. per kilo. These patients had far advanced tuberculosis with cavity formations in many instances and no other treatment had helped them. They had little chance of survival with any other form of therapy. With the advent of iproniazid things have changed in pulmonary tuberculosis. At present we deal very little with this far advanced type of disease. Formerly we were happy to see even a small percentage of cases cured of tuberculous infection, but at the present time we are not dealing with such extensive diseases and the death rate is much smaller. For example, in the 1957 statistics of the U. S. Public Health Service, there were reported only 7 deaths per 100,000 population. We therefore can be assured that the toll of pulmonary tuberculosis is very much less than it was before November 8, 1952. At one time there was little difference between treatment with iproniazid or isoniazid. The results were about the same.

| *Drug* | *Dosage* | *Cases* | *Sputum Conversions* | *%* |
|---|---|---|---|---|
| Iproniazid | 4 mg/kilo | 101 | 26 | 26.7 |
| Isoniazid | 4 mg/kilo | 62 | 16 | 25.8 |

Therefore, at the onset, it made no difference whether we used iproniazid or isoniazid. In pulmonary tuberculosis we found that using isoniazid we had the same results and avoided the frequent complication of hemoptysis that occurred in the cavitary cases when iproniazid was used. We therefore swung to isoniazid.

However, in disease of the bone we had the opposite result. Dr. David Bosworth, who has charge of these subjects in Sea View Hospital, found that in bone tuberculosis good results occurred chiefly with iproniazid. There is a choice between the drug depending on whether bone or lung is involved.

In the early stages of pulmonary tuberculosis experimentation, good results were obtained with either iproniazid or isoniazid, but because of the safety factor we switched to isoniazid. Our chief problem was the dosage of iproniazid, and a great deal was used in pulmonary tuberculosis at 4 mgs. per kilo —a dosage far greater than the 50 mgs. daily used in psychiatric cases. I must therefore state that although occasionally we had complications when we used large doses of iproniazid, these happenings would not be as common in the dosage used in psychiatry. It is my impression that the percentage of complications would be very small.

Whenever we noted any changes upon using iproniazid (Marsilid), we tried to avoid the side effect due to drug toxicity by reducing the dosage to one half or less. The side effects usually disappeared. Of 175 patients on this therapy, only one death occurred during treatment. There were seven deaths in 101 patients. Two patients died of massive hemoptysis. A third patient had extensive bilateral pulmonary disease. After reversal of a progressive toxic course he had a fresh bronchopneumonic infiltration and died. The X-ray previously had shown no new infiltration and this represented a fresh tuberculous bronchogenic spread. Thus three patients died of their tuberculous disease. Autopsy in a fourth patient failed to reveal a cause of death. A fifth patient was a 70 year old who died of acute myocardial infarction. A sixth suffered from severe pulmonary insufficiency secondary to fibrosis and emphysema before therapy. His marked dyspnea at rest was not improved during therapy and he died of pulmonary insufficiency. The results of autopsy were consistent with the clinical state. A seventh patient developed unexplained subacute shock. Autopsy showed, in addition to his extensive pulmonary tuberculosis, a bronchogenic carcinoma, with death due to perforation of this neoplast into the mediastinum.

*Conclusion:* I have just reviewed the cases back to the months before 1952, and I find I cannot concur with individuals who believe that more than 50 mgs of iproniazid is dangerous. My experience has chiefly been in pulmonary tuberculosis, and naturally this is all I can speak of.

# Iproniazid in Orthopedics

DAVID BOSWORTH, M.D.

In the late Spring of 1951 an exciting new chapter in therapy was begun by Robitzek, Selikoff and Ornstein at Sea View Hospital. They began the clinical investigation of the use of isoniazid (Rimifon) and iproniazid (Marsilid). The results as regards the treatment of tuberculosis became so impressive during the summer that the investigation was extended from the Medical Service where it was begun, to other services in the hospital. Since it had already become known by fall that Marsilid was the more toxic of the two, a supply of this chemical was made available to the Orthopedic Service for investigation. Though some few cases were later treated with Rimifon (isoniazid) by the Orthopedic Service, the first investigation began with Marsilid (iproniazid). To avoid the confusion of similar names, we shall continue with the trade names of Rimifon and Marsilid to denote the drugs.

Beginning with the use of Marsilid in October 1951, by the end of January 1952 not only were the dramatic effects of the drug evident as regards the treatment and control of tubercular bone and joint lesions, but the dramatic side effects, some of them toxic, were appreciated. An early report was made and published as of that time in the Sea View Bulletin. Throughout the rest of 1952 further intensive investigation was done not only at Sea View but at St. Luke's Hospital in New York, on orthopaedic cases. Extensive laboratory work was carried out, including such tests as circulating eosinophiles and 17 ketosteroids. All laboratory work showed no alteration from the normal except for a slight lowering at times of the blood platelets. While this intensive laboratory work was carried out, since it was being done on the Orthopedic Service, no notation was made as to the effect of the drug on blood pressure. Aside from this effect, most of the other effects now known were appreciated by the latter part of 1952 and recorded in the literature.

On dosages of Marsilid of 4 mgs per kgm it was noted that a percentage of psychoses occurred after four to six weeks' use and that such psychoses were reversible in their entirety on cessation of medication. Euphoric reaction was especially appreciated but because of psychoses that developed, no attempt was made to use the medication to produce euphoria in depressed patients. This remained for the psychiatrist to explore and exploit at a later date.

It was found that Marsilid was present in the spinal fluid in approximately 50 per cent greater concentration than in the blood serum. Therefore, we felt that when maintaining satisfactory serum levels side actions occurring (psychoses) might be unavoidable in order to maintain such blood serum levels. Gradually, at a later period, we came to the conclusion that lower dosages of the drug could be effective, although the action as regards tuberculosis was slowed down.

Now with the drug begun at 4 mgs per kgm of body weight where necessity warrants, and within a few days reduced to 2 mgms per kgm of bodyweight, euphoria is still noted but psychosis is rarely seen.

Liver toxicity was known to be one of the dangers of the use of Marsilid from laboratory experiment preceding its clinical use. We therefore did intensive studies of the effect of Marsilid in producing liver toxicity in patients. From our experience throughout we have failed to see any permanent liver toxicity incident to the use of Marsilid. There have been minor elevations of liver function tests in a few patients which have varied from time to time on continued medication at the same dosage. No specific instance of jaundice has occurred which was not related to other possible factors such as stoppage of the common bile duct by retroperitoneal abscess, or serum jaundice from preceding transfusions, etc. In one instance with a Laennec's cirrhosis where infection existed resistant to all antibiotics, Marsilid was used without any change in the basic Laennec's cirrhosis or any aggravation thereof. This, associated with our negative experience as regards liver damage, seemed

to indicate that if such damage does occur it must be rare and due to idiosyncrasy in the individual patient.

Of the six patients originally submitted to this drug for investigation, all were chosen because of their evident intractable tuberculous orthopaedic lesions and their probability of demise. To date, only one of these patients died. He had eight bone and joint tuberculous lesions, was tremendously emaciated and died seven weeks after institution of Marsilid therapy, in a markedly improved condition, with five of the lesions healed. He was overwhelmed with his disease.

It was early appreciated that not only was there control of early tuberculous infection but that euphoria was secured, pain markedly relieved, weight gain induced, temperature with infection promptly reduced, and wound healing obtained regardless of the fact that many of the sinus lesions contained not only the tuberculous organism but many other forms of bacteria. It was also early appreciated that decalcification of osseous struture of noticeable extent appeared to take place within three months. A translation of these benefits and of the osseous decalcification was attempted for a specific end in patients with other than tuberculosis.

Decalcification was attempted, used and is now continued in use to remove sclerosis of infected bony structure so that contained sequestra may be appreciated. The use of Marsilid in addition to antibiotics, and in cases where organisms were resistant to all antibiotics, has been studied and proved of considerable help in treatment. This includes cases of old osteomyelitis, fresh osteomyelitis and when metal implants used in the reduction of fractures became infected.

Weight gain has been obtained in emaciated patients. It is a question whether increase in weight is attained by the normally nourished person who takes Marsilid. An instance of weight gain in an emaciated patient occurred in one patient who had had a gastrectomy a year previously and when placed on Marsilid gained 20 pounds in three weeks. Weight was lost when Marsilid was stopped and again occurred on re-instituting therapy. Finally, her weight was stabilized on 50 mgs of Marsilid a day and has maintained satisfactory recovery.

In order to determine the effect of Marsilid in the relief of pain, it was desired to get away from the specific action as regards infected states. Therefore, its use was attempted in metastatic tumor lesions. It was found that some euphoria was produced in patients with carcinomatous metastatic lesions, and mild pain relief. In metastatic lesions of mesodermal tumors the pain relief was dramatic and continued with the use of Marsilid accompanied by moderate euphoria. No influence as to the tumor itself or its progress was demonstrated and all such cases terminated in the usual manner.

By chance one patient who had a lupus erythematosus was treated with Marsilid for another condition and the lupus erythematosus cleared up and has remained quiescent since. Other cases of acute lupus erythematosus have been similarly treated with similar satisfactory results. The chronic lupus erythematosus has been noted to improve, though the deep scarring remained. On this basis and with the knowledge that lupus erythematosus is one of the collagen diseases, plus the fact that no keloids were seen to develop in operative scars in tuberculous patients being treated with Marsilid, the drug was used for keloids resistant to x-ray and recurrent on excision. This has been moderately successful as to the reduction of the size of the keloids and markedly successful as to reduction of the burning, itching and other sensitivity experienced by the patient. Not enough cases are at hand to be certain what the action is in this direction, or as to the length of the benefits secured.

Since Marsilid seems to have a marked metabolic effect, we surmised that it might be used in gout. In the three patients in whom we attempted its use for this condition, failure ensued. This suggests to us that if one uses Marsilid for a specific beneficial effect noted, namely—relief of pain, weight gain in emaciated patients, wound healing (as an adjuvant), temperature reduction where infection exists and control of sclerosed osseous lesions, success may be expected in a satisfactory percentage of instances. The use of this drug along the above lines provides quite a wide spectrum of diseases in which it may be employed.

# Discussion: Is Marsilid a Dangerous Drug?

*Dr. Mattia:* It is rather difficult to draw any conclusions with a drug that behaves as this one. It is difficult indeed to seek out the answers since in any group of patients significant changes will be found. Unless you can get a series of tens of thousands of patients the results will not be statistically significant since the incidence of hepatic complications is so low. For example, we did take a group of 30 patients in one study. Before we started treatment some of them had elevated transaminase levels, others had normal transaminase levels, and some had low levels. The results were highly variable and inconclusive. Some of the levels came down while on Marsilid therapy. Some of the levels went up. It certainly provided no help as to what was happening. We do feel today, though, that either the serum transaminase or the isomerase levels are probably the best test to employ but we would not want to state that positively. We are continuing these big batteries of tests at several institutions, trying to find out which tests are best. I think the experiences of the doctor were certainly the experiences of some of the other physicians who have reported to us.

As to treatment, your experience with ACTH has been the experience of another physician in England who recently reported that a seriously ill patient did well following ACTH. On the other hand, I had contact with a patient who was doing extremely well, was about to be discharged when the physician began Cortisone. The patient suddenly went down hill. It makes me wonder and suggests that we should move cautiously with steroid therapy.

Rheumatologists who have had considerable experience with this drug invariably give steroids with Marsilid and for some unknown reason they have not observed any serious hepatic complications. One should be guided by the particular problem and employ the usual therapeutic measures when hepatitis develops. It is too early to draw any conclusions as to adequate therapy.

*Dr. Nathan S. Kline:* "Dangerous originally meant power, control. The current usage means full of risk, perilous."

In the dictionary of synonyms Mr. Webster says: "Dangerous is defined as applied to persons or to things that should be or are treated with exceeding care because contact with them or use of them is unsafe."

On the basis of Webster's definition I would certainly give a very hearty no as the answer to our subject question "Is Marsilid a Dangerous Drug?" Marsilid is not a dangerous drug in the sense of being something that one should avoid using. It is true, certainly, that it is a potent drug which carries with it the caution that it be used with care.

Our difficulties, I think, arise in part from the fact that the original so-called tranquilizers had extremely low toxicity and many practitioners fell into the habit of regarding them as innocuous preparations, with which one was unlikely to do any harm. When Marsilid came along, it was treated in much the same manner and most of the difficulties in my opinion arise from the fact that the drug is not used with the respect due it.

I think Marsilid is certainly the most potent of the psycho-pharmaceuticals that have come along to date, that it is probably in terms of usage, in a class with a drug like digitalis, or insulin in the treatment of diabetes. Further, it is a drug which requires individualization of dosage. One can start off at various levels but one cannot put the patient on the drug and go on a two months' vacation and assume that everything will be fine when the physician returns.

As to side effects, the question of liver toxicity is one on which we ventured opinions in the past. There is a very curious fact which has been pointed out, that apparently the incidence of liver reactions in the schizophrenics is considerably higher than in other parts of the patient population. I spoke with Dr. Selikoff about it a few weeks ago and he mentioned they had run 11,000 liver function tests at Seaview Hospital and I believe he said none of them had shown any abnormality. In contrast, we have run several thousand at Rockland State

Hospital as baseline studies prior to placing the patients on drugs of any sort. We routinely use four liver function tests on each patient, repeat each of them at one week intervals. Our findings to date indicate that roughly one out of four tests at least is outside of the normal range in 85 per cent of the schizophrenics. So one has a right to raise questions as to whether the liver itself may not be primarily or secondarily involved in the schizophrenic process. It also emphasizes the fact that studies which are done, in which base lines were not obtained, in patients of this type, are practically worthless.

The finding of a positive liver function test if you don't know what it was before means nothing. You have no right, particularly in psychiatric patients to assume that it is within normal limits. In private practice probably the hypotensive effect is more annoying than is the rare danger of liver toxicity, and the use of one of the stimulants, amphetamine or others of the psychomotor group seems to help in countering this.

The reason, I gather, people talk about other aspects of the use of Marsilid is that there is little to say on the specific question of being dangerous. We still feel the 150 mg. dose is preferred as the starting point in most cases and I would certainly concur with Dr. Mattia that we have seen no evidence that the high dosage induces more toxicity than does the low dosage.

We feel further that as soon as the patient begins to show a favorable response the drug should be reduced. This is our method of treatment: to start with high doses and after a response, to cut down.

The other procedure is slightly illogical, if the pharmacology is correct. Marsilid is a cumulative drug and presumably favorable effects are not obtained until the required blood level is reached. The rational thing to do is to reach the suitable blood level as rapidly as possible and then to maintain it by proper dosage. I have seen at least half a dozen private patients treated at the start with 50 mg. without response and upon raising the dose to 150 mg. showed very satisfactory results. I am not convinced on evidence that has been presented here or elsewhere that this is not the proper way of administering the drug.

I would further disagree with my good friend, Leo Alexander, as to his designation of what one might call broad spectrum antipsychotics. I think that the use of Marsilid is not nearly so specific as his remark would seem to indicate.

It is our feeling that there are in the class of what we have called psychoactivating drugs three principles of drug action, first, the psychomotor stimulants, second, what we have designated as psychostimulants, which have the effects of stimulating with minimal side motor reactions, and finally, the psychic energizers. They seem to differ considerably in their action. The psychomotor stimulants are easily recognized because of the motor side effects. The differences between the psychic stimulants or psychostimulants and psychic energizers occur at both the psychological and physiological levels. The blood pressure goes up in one group and down in the other. The appetite is usually decreased by the psychostimulants and increased by the psychic energizers. The psychic stimulants, if given in adequate doses are, more rapid in their onset and also are easily given in a sufficient dose to produce euphoria. Euphoria with the psychic energizers is extremely rare. In the few cases that I have seen, it usually occurred after someone has had a prolonged depression which is relieved by a psychic energizer and there was a rebound phenomenon for a matter of a few days or a week in which the patient was euphoric, I think, more on the basis of relief from the depression than from any direct action of the drug. Larger doses of psychic energizers do not seem to bring about euphoria. You reach a certain level and there you stay, regardless of the dosage. This is not true of either the psychomotor stimulants or the psychostimulants.

I would further point out in a depressed patient there are three ways of relieving depression. I think that this has led to some confusion. There is obviously the group of psychic stimulants which would include psychomotor stimulants and psychostimulants, which act to cause increased reactivity, usually pressure of speech, flight of ideas, the other characteristics that go with overstimulation. Sometimes if the de-

pression is not severe the patient can be temporarily brought up to a functional level with psychic stimulants. If the patient's recuperative power is good, he may be able to hold the gain. However, if it is not good then even with continued use of the psychic stimulants the patient falls back. There is an exhaustion apparently of whatever reserves the patient has. Once these reserves have been used up, the psychic stimulants fail to produce any reaction.

With the psychic energizers this is not the case. The usual signs of overstimulation are absent. The patient even after long usage retains the effect. We now have patients on this type of drug for almost two years and there is no evidence that their effectiveness has worn off.

The third way of relieving depression is, I think, what has caused the most trouble. Some patients who have most of their energy bound up in the neurotic, psychotic process, if given appropriate ataractics or even sedatives are often able to release the bound-up energy and the patient clinically shows relief of depression. This, however, is by an entirely different mechanism than with the first two types of drugs.

*Dr. Leo Alexander:* Dr. Kline has brought up the important point of psychophysiology. There are various ways in which a depression can be treated. I would like to call one process an extinctional process. You can either treat depression by extinction or do it by what you call energizing. Electroshock certainly works by the extinction process and this therapy has been uniquely effective. Morphine or derivatives are the oldest treatment for depression. That is an extinction process. Lewenhock as early as 1931 used atropine intoxication and used the activating process. These two approaches will always be with us and the important thing is to decide which to use. Depressions are different. We can distinguish group types and groups of depressions and I thought that Marsilid is particularly good in the inert type while the extinction treatment is more useful in other types.

*Dr. Eugene R. Jolly:* In the past few months we have had a great deal of interest in the subject question and despite what I have heard tonight I still think it is a problem. We have to be realistic. We have heard statistics. They would indicate that the drug is no more dangerous than many other drugs that are on the market. Nevertheless, as we are all aware as clinicians, each statistic is an individual. We have studied Marsilid and we have studied the problems of the side-effects of Marsilid since 1951, when it was first brought to our attention. We were aware of its potential side reactions. We were wary of them. Dr. Ernie King contacted individuals who had been working with this drug in the field of tuberculosis and in other fields and talked to them. The process of evaluating this drug extended over a period of three years and it was not till 1955 that the Food and Drug Administration released this drug to the clinicians for public use. It was realized that it was potentially a dangerous drug and I use that word advisedly. We recognized the fact that it had many adverse effects. We recognized that hypotension in some cases could be severe. We recognized that motor stimulation occurred in many patients on high dosages. We recognized that it had many other side-effects. These cautions were reflected in the brochures that were authorized for distribution.

Since the very beginning, close supervision of the patient has been recommended. This has not been continued throughout the years. We felt, however, that the drug was a very important agent in tuberculosis. On the basis of Dr. King's personal interviews and on the basis of the material we had at hand, we did not recognize hepatic toxicity as a potential danger with this drug. There were scattered reports of hepatitis throughout this period. They were not associated with Marsilid. They were few in number. The animal toxicity studies that were submitted with the drug did not indicate that the drug was potentially hepatotoxic.

In February of this year we became acutely aware of the problem, when the gentlemen from Hoffmann-La Roche were kind enough to come to us and furnish us with data showing that there had been some cases of hepatitis reported with this agent.

I want to say right now that since that time the co-operation with this firm has been excellent. They have furnished us with material at our beck and call. We have had absolutely no problem in obtaining any data which Hoffman-La Roche had available.

When one receives data of this sort, and we frequently do, with many drugs, the first thing that one considers is association, since case reports such as we receive very seldom completely indict a drug. But we must worry about association and when association with the drug and a particular reaction becomes excessive, then we must assume that there is a problem and we must decide what to do about it.

The process of evaluating the side effects from Marsilid, particularly this side-effect, took a period of about a month. In the early days we were not convinced that the drug could produce hepatitis but we did not debate that fact. What we were interested in was efficacy. Classically the Food and Drug Administration does not rule on efficacy but whenever there is a problem of toxicity then of course efficacy and safety are tied together.

We may release a drug which is potentially toxic if it is efficacious. We would be derelict in our duty to deny the public a drug which is quite efficacious for the reason that it may produce an occasional lesion of some important tissue. This was the problem and this is the tack we took.

In the majority of cases I became convinced that the drug was efficacious. I should restate that. In the majority of the interviews that I had with clinicians and investigators, it was apparent that they felt that the drug had utility in the sphere of which we are talking. However, to complicate the problem, I must state that the opinions range from extreme negative to extreme positive. They ran the gamut of those who felt the drug was useless, extremely toxic, to the other extreme where one had the idea that this was indeed not only a revolutionary drug but one of the greatest drugs ever produced. So with such conflicting opinions one has to decide which is right. Either may be right but the chances are a happy medium exists. In selected cases this drug may be useful.

We feel, in the Drug and Food Administration, at the present time, on the basis of information that we have at our disposal, that the drug should be used in those patients in which the anticipation of therapeutic benefit outweighs the risk involved in using it. We must be realistic. We must recognize the risk. One per ten thousand does not seem like a high figure.

May I, however, make a statement that we are by no means sure of this figure. The incidence could be higher. It could be as high as one per thousand. It could be higher than that. On the other hand, it could be lower. The statistics that we have are not accurate enough for us to make even an approximate evaluation of the risks involved in regard to hepatic toxicity.

*Dr. Leo Alexander:* I might just ask the first question. I have seen two cases in which non-jaundice liver damage occurred, which seemed to be an interference with the galactose mobilizing function of the liver, appearing as a sort of hyperinsulinism, flat sugar tolerance curve. I wonder whether anybody else has seen that. Dr. Mattia or Dr. Bagdon, have you seen any interference with liver function other than jaundice, namely, galactose mobilizing function of the liver producing a flat sugar tolerance curve?

*Dr. Bagdon:* I can answer for the animal data, we have seen no alteration in carbohydrate metabolism in animals.

*Dr. Train:* Including the list of complications, I did not see mention of any complications pertaining to myocardial infarction, hypertension, or severe vascular disorder. I have one case of myocardial infarction due to Marsilid, which was reported in Montefiore Hospital a few months ago. I have seen roughly five cases, five individuals whose blood pressure went up from 110, 120 to 180, 190 in a few weeks. I have seen at least seven or eight patients with poor circulation in the lower extremities, one patient who developed severe edema, not ankle edema but edema around the toes, dorsum of the foot, ecchymoses, and so on. I have not seen a single case of toxic hepatitis. I have seen many cases with severe vascular disorders and patients with disturbances of blood pres-

sure; hypotension in many cases; hypertension in a few cases and great lability of blood pressure, varying from hypotension to hypertension in a number of patients.

*Dr. Theodore R. Robie:* I have seen one case of temporary hypertension. That case was proven to be due to the excessive degree of constipation and relieved within a period of two days when adequate catharsis was induced. I have reported universal hypotension. With people who are normotensive to begin with, there is very considerable degree of hypotension. I agree with Dr. Kline that we should start with a dose of 150 mg. In an occasional case where we are a little fearful we may start with less.

I wonder if in these cases that have been reported there was a factor of excessive constipation. Everybody knows that the drug produces increased constipation and if it is not watched you may get new troubles. It was pointed out, that somebody in Boston is using saline cathartics with success.

*Dr. V. J. Mattia:* I was intrigued by the comments about treating constipation induced by Marsilid. I remember when the ganglionic blocking agents first came out for the treatment of hypertension one of the problems was the sudden drops in blood pressure which occurred from drug accumulation in constipated patients. The newer ones such as mecamylamine are completely absorbed orally so drug accumulation is seldom encountered.

I am also somewhat interested in Dr. Train's observations that Marsilid caused a myocardial infarction in a patient. It is certainly true that for decades we have accepted the theory that marked reductions in blood pressure in patients with coronary artery disease may induce an occlusion. I would be hard put to state emphatically from experience in one patient that any drug or drugs was responsible for the development of a coronary occlusion. It seems to me that it will take more time before you can conclude that the occlusion which developed during the course of therapy was due to that drug.

*Dr. T. R. Robie:* I would like to know what is the safest way to control the edema? Why do we have the edema anyway?

*Dr. Mattia:* It should be pointed out, first of all, that we don't know precisely why edema occurs. We wish we had this answer. It may be that with Marsilid we are permitting serotonin to circulate longer. Serotonin apparently has antidiuretic effects. Electrolyte alterations are apparently not responsible. It is not due to the electrical discharges for we have followed these patients very carefully.

As to the treatment, in most cases reduction of dosage or discontinuation of therapy promptly clears up the edema. We certainly have had many recommendations on the effective use of chlorothiazide but I assume that other diuretics will work equally well.

*Dr. Jolly:* I don't believe anyone has the answer as to why the edema occurs. This is a side effect which has occurred and no one has ever given a reasonable explanation for it. Of course Diural and similar substances are not innocuous and in some cases produce central nervous system effects.

*Dr. Ornstein:* We rarely had that complication. It may occur but we did not see it in our 101 cases.

*Dr. Charles Buckman:* I do not want to talk about edema in particular. We have had two cases of severe jaundice and they both came on very rapidly, within 48 hours. One ended disastrously but the other one is coming along all right. In each instance we were not able to detect the situation early by any of the known liver function tests. However, we are able to detect liver pathology in say, chlorpromazine or some of the other drugs. I am wondering whether there is any test that we can do to foretell liver damage caused by Marsilid, as we can with ataractic drugs.

The other point is that in the jaundice, the first clinical sign of trouble seems to come roughly 24-48 hours after administration. Is it possible that the cumulative action of the drug causes it?

*Dr. Alexander:* I think that prevention of liver damage and the treatment is the central problem. As to the prevention, I don't know, although we now do liver tests

before putting patients on treatment. In one particularly severe case of the three that occurred the patient did very poorly. She was close to moribund. Giving ACTH seemed to pull her out and she made an uneventful recovery.

*Dr. Bagdon:* We did take a group of 30 patients and before we started treatment some of them had elevated transaminase, others had normal transaminase, some had low normals. Some of those who were elevated came down while on Marsilid therapy. Some of the normals went up. Some of the subnormals went up. Some went even lower. It certainly provided us with no help as to what was happening. We do feel today, though, that either the serum transaminase or the isomerase levels are probably the best test to employ but we would not want to state positively that this is so. We are merely continuing these big batteries of tests at several institutions, trying to find out which one will be efficacious. I am inclined to agree that in the fair number of patients the course is extremely rapid. I think that the experiences related here were certainly the experiences of some of the other physicians who had reported to us.

As to treatment, it was reported by another physician in England recently that a patient seriously ill from the effects of Marsilid did recover with ACTH. On the other hand, I had a personal contact with a patient who was doing extremely well, was about to be discharged and the physician began cortisone and the patient suddenly went down hill.

On the other hand, rheumatologists, who have had considerable experience with this drug, invariably give steroids with Marsilid and for some reason they have not observed any cases of hepatitis. I think the best thing is to be guided by the particular case and to use the usual measures when hepatitis does develop.

*Dr. Kline:* We have not had too much experience with the steroids because, thank goodness, we have not needed it, but Douglas Goldman in Cincinnati has reported the use of 12.5 mg. of cortisone once or twice a day, particularly if there is severe hypotension. He continues the Marsilid, adds the cortisone and finds it extremely effective.

As far as what is happening is concerned, we have published a number of times that the reserpine and phenothiazine derivatives reduce resistance to infection and this has also been observed in animals. If the patient on either reserpine or a phenothiazine, develops a bacterial infection, he usually has it more severely and needs more vigorous treatment. This is true with these patients in respect to diabetic crises, cardiac decompensation or almost any of the ordinary medical disasters. We have not, however, noticed anything unusual about response to viral infections. It may be that this is what is going on with the Marsilid; that there is resistance to viral infections, just as there appears to be decreased resistance to bacterial infection with the drugs which do the opposite. It makes a nice counterbalance, anyhow. There is probably a cumulative effect with at least some evidence that liver function in many of these patients is disturbed to begin with. The added factor is that possibly resistance to viral infection is lowered. By way of prophylaxis if this is true, one might be able to use gamma globulin as suggested by Dr. Barondess. Obviously in an area where there is any epidemic of infectious hepatitis, Marsilid should not be used until the epidemic subsides.

*Dr. Bagdon:* I would like to say in regard to the animal studies that we have not seen liver toxicity even when very high doses have been employed. A large part of our research program in the toxicology group is devoted to finding a sensitive liver function test which is not currently used. Presently we are emphasizing serum transaminase. We hope to enlarge the research program to include other enzyme systems which might reflect liver function.

*Dr. Bosworth:* The case we saw that had jaundice was the case I showed you due to mechanical pressure. We noticed it in the first 137 cases. We ran three liver function tests continuously every week for several months and we got some minor alterations in liver function, and finally we came to disregard them. We saw those things fluctuate, sometimes a little rise, and sometimes

down again and we got to paying no heed at all to them. We also had a case of Laennec's cirrhosis, which was pretty bad, because of resistance to infection. We healed the infection on Marsilid, got no change in liver function test, despite the Laennec's cirrhosis. We took the patient off the Marsilid and saw no change in the liver function test and now the patient is on 2 mg. per kilogram. We don't fear permanency of damage to the liver. There may be some toxicity from time to time which is added to the toxicity of their diseased bodily condition. We don't fear any permanency in this. Our total number of cases is now approximately 500.

*Dr. Alexander:* I agree with what Dr. Bosworth said. This one case is anecdotal. This was a patient of the central nuclear group. This man had 57 electroshocks without improvement. He was really an inert type. He had an abnormal liver and was like these types of depression. He ate all day, slept most of the time and could not go out and work for five years. In desperation we saw no other hope for this man. He was put on Marsilid and he has done beautifully. He is now selling automobiles. So that in this case we really took a calculated risk.

*Dr. Mattia:* In England recently one of the foremost hepatologists reported on her experiences administering Marsilid to eight patients with severe liver disease. The patients did not show an improvement in their mental state but interestingly enough in none of the patients did the hepatic state become more sever.e Some of these patients were even in hepatic coma.

In addition we have had physicians report on the treatment of chronic alcoholics with severe cirrhosis who have not had an aggravation of the underlying liver disease. These incidents are mentioned to point out how perplexing the problem is and how difficult it is to draw any conclusions. However, it is my opinion that Marsilid is contraindicated in the presence of liver disease.

*Dr. Alexander:* In my case the medical consultant told me facetiously he disapproved of euthanasia. I said, "Not euthanasia. I was merely taking a calculated risk." It worked out.

*Dr. Ornstein:* May I say in the 101 cases on which we reported we did liver tests repeatedly. Even when there was evidence of liver damage, it was never treated. They were all free of and never developed any liver disease.

*Dr. Alexander:* How many deaths have been reported from Marsilid use?

*Dr. Jolly:* There has been reported to us to date 33 out of a total number of cases estimated at, I would say, approximately 400,000 plus or minus 50,000. I do not make any statement that these deaths were due to Marsilid. This is merely the association rate.

*Dr. Train:* I have to qualify "patients." I gave Marsilid to several terminal cases, one of whom died when given Marsilid. I don't know if the Marsilid accelerated the end.

*Dr. Alexander:* We should limit the description "to previously healthy depressed psychotic patients."

*Dr. Kline:* It is important that those who have had poor results with Marsilid should take into consideration that the drug is an extremely strong potentiating agent. Using other medications at the same time can completely nullify the beneficial effects of Marsilid. Doses of any of the phenothiazines have to be radically reduced. Many of the poor results that I have seen are with patients who were on other medications such as hypnotics. Sleeping medications at times will give a hang-over for two or three days. Patients not removed from, or given greatly reduced doses of other medications cannot be properly evaluated. Failure of response should lead to close inquiry as to whether other drugs, irrespective of the smallness of dose, may not be interfering. There is also the paradox that at times excessively large doses of Marsilid alone may produce lethargy. As indicated previously, individualization of dose is the key to successful treatment. Contrary-wise there are cases where the reverse happened. There are, then, other factors involved. It is all a matter of the manner in which cases are selected. In the institutional setting this is altogether different from the method that may have to be used in private practice. For instance, the

agitated depressed patient, who is a suicidal risk is a source of great concern within a family group. With such a patient one cannot afford to wait three or four weeks. Also, putting aside the environmental factors, the manner in which we ordinarily are accustomed to extract cases for a specific mode of treatment has to be considered. I think that Deprol may possibly be useful in the management of the neurotic depression. My experience, on the other hand, with the management of a depression that requires shock treatment is altogether a different story, and while Marsilid *is* effective, our early work with Deprol would not support its use with more severe cases.

*Dr. Alexander:* My experience would indicate that the more neurotic patient, a type three, rather than a type six, is a candidate for Marsilid use. This drug covers an entirely new and specific area in the spectrum of depressive and pseudo-depressive illnesses.

*Dr. Hand:* Of course the more neurotic is not the type of patient in the first place who has responded well to shock therapy.

*Dr. David Impastato:* I should like to make an observation. The death rate with Marsilid is reported as less than one in four thousand patients. On the other hand, the death rate in electroshock therapy is one in one thousand patients. From these observations, insofar as the complication of death is concerned, it appears safer to use Marsilid than electroshock.

*Dr. Alexander:* One cannot be sure that the death rate with iproniazid is one in four thousand. My rate is one death in fifty-two patients. Three patients in addition had severe liver damage.

*Dr. Impastato:* In estimating the death rate we cannot consider a small number of patients treated by one doctor. We can accept as valid only the overall rate based on the treatment of a great many patients.

*Dr. Jolly:* I do not think that we have a valid statistical evaluation of the death rate with Marsilid. Right now it would appear that Dr. Impastato's evaluation is correct.

*Dr. Hand:* I would like to point out one factor that has not been mentioned in connection with jaundice. In the management of patients, we have been giving many injections. To what extent has there been a transmission of jaundice by the use of improperly sterilized needles?

*Dr. Alexander:* This is an important point. In a study made by Dr. Seel at the Beth Israel Hospital, he traced much of the jaundice to the injections. For this reason I think a good study on the occurrence of jaundice after Marsilid medication must take this fact into account.

*Dr. Gahagan:* I have made several inquiries about Marsilid from many reliable sources. I will refer to two of the replies. Dr. Eugene R. Jolly, New Drug Branch, U.S. Department of Health, Education and Welfare, who was one of the speakers at the meeting, writes in a letter, dated July 23rd, that "there have been reported to us to date 180 cases of hepatitis associated with Marsilid therapy with, approximately, a 20% mortality figure."

In a letter, dated July 22nd, Dr. Henry Brill, Assistant Commissioner, New York State Department of Mental Hygiene, writes: "The Department of Mental Hygiene institutions in New York State ceased using this drug at the time of the recent unfavorable publicity. Previous to this it had been under trial in various conditions and in dosages up to about 150 milligrams per day. There were a number of cases of jaundice and the newspapers reported two deaths in our cases which we reported to them when they became interested in this entire matter."

It is my opinion that the use of Marsilid is not justified because of the severe and sometimes fatal liver injury which the drug may induce. Or, perhaps, this might be modified by saying that its use is justified only when EST and other accepted therapeutic measures have failed.

# Suicidal Risk in a Municipal General Hospital

JACOB H. FRIEDMAN, M.D., and REMO CANCELLIERI, M.D.

Suicide is considered an anti-religious act and bears social stigma. Attempted suicide is punishable as a crime in England and in some jurisdictions of the United States. The stigma attached to suicide appears so overwhelming, that there is no mention of such a category in the latest edition, 1952, of "Standard Nomenclature of Diseases and Operation." However, in psychiatric diagnoses, under manifestations, suicide can be recorded. To our knowledge, in annual hospital reports, suicidal attempts are not mentioned. It is therefore difficult even to estimate the number of suicides that occur annually. Nevertheless, Karl A. Menninger[1] states, "once every minute or even more often someone in the United States kills himself or tries to kill himself with conscious intent. Sixty or seventy times every day these attempts succeed." On the other hand, Oliven,[2] quoting the United States Public Health Service and the Metropolitan Life Insurance statistics, states that about 100,000 suicidal attempts are made annually in the United States, of which 16,000 are successful. When suicide does occur, the family tries to conceal the fact. However, if a patient is in a hospital at the time of suicide, the family frequently projects the blame of the suicidal act on to the hospital. The hospital is then subject to a malpractice suit, it being claimed that the patient was mentally or emotionally ill, and insufficient precautions were taken to prevent such an act. The psychiatric hospital is constructed, designed, equipped and medically staffed to recognize and treat the potential suicidal patient. Despite these elaborate precautions, 32 suicides were reported in ten thousand admissions in a state hospital for the mentally ill, between 1936 and 1949.[3] Banen[4] reports 23 successful suicides at the Veteran's Administration Neuropsychiatric Hospital at Bedford, Massachusetts, between 1928 and 1953, but 12 of these patients were on furlough or on pass from the hospital.

From the Neuropsychiatric Service, Fordham Hospital, New York City, N. Y.

There is a trend toward psychiatric units in the general hospital, but the psychiatric unit remains separate and apart from the rest of the hospital, and the psychiatric patients are kept under maximum security. Paradoxically, despite the suicidal risk, a few progressive administrators of mental hospitals are unlocking the wards housing the disturbed patients, making the entire mental hospital a so-called open-door hospital, with gratifying results.[5,6]

A marked fear of the hospital administrator, both in the psychiatric and the general hospital, is the suicidal potential of the psychiatric patient. Elaborate provisions against suicidal attempts are routine in the mental hospital. When a suicide does occur, detailed investigation always follows to determine if there was any negligence by personnel or insufficient precautions. Such procedure guards the hospital from bad publicity and serves as a defense against a malpractice suit.

The municipal general hospital cannot provide on its wards the elaborate precautions taken by the mental hospitals to prevent suicide, especially when no distinction is made as to grouping of patients in relation to mental and emotional status. In such hospital, if a patient is suspected of being suicidal, he is placed near the nurse's desk, with rails on the sides of the bed. These are the only practical precautions taken in a municipal general hospital in respect to the suicidal patient. It is generally believed[7] that once a person actually attempts suicide, he is a potential repeater. Therefore, we have taken as our criteria of suicidal patients, those who have attempted previously to take their life.

We reviewed the charts of all patients in Fordham Hospital from 1954 through 1957 who were admitted for ingestion of poisons, such as, barbiturates, paraldehyde, Miltown, Separine, Thorazine, aspirin, Anacin, Demerol, morphine, heroin, codein, atropine, benzedrine, potassium permanganate, sodium

fluoride, iodine, mercurochrome, bromides, insecticides, furniture polish, cleaning fluid, rubbing alcohol, shaving lotion, gasoline, ammonia, lysol, lye and arsenic. There were ten cases of asphyxiation by carbon monoxide. Although there were patients who attempted suicide by the use of firearms, stabbing, jumping from windows, hanging, automobile accidents, and drowning, we were unable to recognize this type of patient, except four who attempted suicide by cutting their wrists.

Analysis of Data: From 1954 through 1957 a total of 272 patients had attempted suicide prior to admission to Fordham Hospital, 22 died. The family signed out 154 against advice, with the understanding that the patient would have the necessary psychiatric care; 37 patients were discharged to their own care, as they were considered a hysterical type of individual, with the advice that they seek psychiatric care. All these suicidal patients, after they recovered consciousness, were seen by the psychiatrist. Although admitted in a comatose state, many denied suicidal attempt and were evasive in giving histories. They stated that they accidentally took the wrong medication, that they were drunk at the time, that they only took one pill, or even denied taking any medication. A number admitted the intent of suicide.

It is notable that not one of these patients made a suicidal attempt while in the hospital, although their stay ranged from one to 21 days, the average being 2.7 days. It might be argued that the average stay of 2.7 days after a suicidal attempt is not sufficient time to appraise the potentiality of a repetition of the act in the near future. However, it must be borne in mind that these patients did not receive any therapy after their recovery from the suicidal attempt. Siegal and Friedman[8] point out that the conscious or unconscious purpose of suicidal threats and serious suicidal attempts is to attain favor, security or other desired outcome against an authoritative figure. Therefore, a masochistic character thus minded, may seek to exact advantage through declaration of intention or even attempt to inflict death upon himself, should his desires be thwarted. They coined the term, "succumbence complex," when the authoritative figure yields to the demands of the threatening suicidal or attempted suicidal individual.

Rubenstein et al.[9] state that they regard attempted suicide, not as an effort to die, but, rather, as a communication to others in an effort to improve his life. They were impressed that of 44 cases, 34 derived changes in their life situation, as a result of attempting suicide. It would thus appear that the unsuccessful suicide attempt will not be repeated quickly, at least not during his hospitalization in the hospital.

We have studied histories of 1269 patients admitted to the hospital from 1954 through 1957 with psychiatric diagnosis which run the gamut of the entire psychiatric nomenclature. No individual or special study was made on this group as to whether they were actually suicidal. However, it is obvious that many were at least potentially suicidal. Their stay in the hospital was considerably longer, the average being 21.7 days. Pollack[1] analyzed the clinical records of 11 hospitalized patients who committed suicide while under medical care and observation at a general hospital. His purpose was to suggest possible clues which physicians in a general hospital setting may use to recognize potential suicide. He concluded that the older male with a physical disability plus an organic psychotic reaction should be considered a suicidal risk and precautions taken. We cannot agree with this study as our group of 606 patients with chronic brain syndrome associated with cerebral arteriosclerosis or with senile brain disease, with an average stay of 33.1 days, did not attempt suicide during their hospitalization. Of the 1,269 patients with psychiatric diagnoses, there was no instance of attempted suicide while in the hospital setting.

During 1954 and 1955 there was no suicidal attempt made by any patient at Fordham Hospital. In 1956 there was one suicidal attempt. In 1957 two attempted suicides were reported.

### *Case Reports*

*C.H.*, age 69 years, male, was admitted to Fordham Hospital on August 29, 1956, from a nursing home, with the complaint of constant pain over the bladder region and a bloody urine. History revealed that he had a transurethral resection for an

epithelioma of the urinary bladder in 1955. During his present hospital stay he was given supportive therapy in the form of anodynes, tonics and hormones. On October 7, at 5:20 A.M., he had conversed with a nurse's aide, and then went into the bathroom to smoke. At 5:30 A.M. the patient had not returned to the ward and a thorough search was made. At 6:00 A.M. his body was seen on the extension of the pharmacy at the level of the first floor, two stories below his ward. He apparently jumped or pushed his way through a kitchen window. He had always been cheerful and alert and had adjusted well to the hospital routine. He showed no evidence of any emotional instability or mental aberration. There was no indication whatsoever, that this patient was suicidal.

*J.P.*, age 78 years, male, was admitted to Fordham Hospital on August 6, 1957, because of weakness and frequent bowel movements. He suffered from arteriosclerotic heart disease. In view of his age he was considered seriously ill and was not permitted out of bed. During his five day hospital stay he appeared calm; he was always rational and able to carry on a conversation. He showed no evidence of any mental aberration or emotional instability. On August 11, at 12:15 A.M., the patient was not found in bed. However, his bed was so arranged, that it appeared as though someone was in it. Both side rails were in place. The unscreened window, next to his bed, was open and his footstool was on the floor beneath the window. His body was found in the courtyard, three stories below. There were no witnesses to the incident and other patients were unaware of the occurrence. Again, in this case there was no indication that this patient was suicidal.

*W.B.*, age 52 years, male, was admitted to Fordham Hospital, August 21, 1957, because of pain in the lumbosacral region, which pain radiated down the right lower extremity. He was hospitalized, previously, for four weeks at St. Luke's Hospital where he had a spinal fusion. He signed himself out from St. Luke's and he was admitted the following day to Fordham Hospital. While at Fordham he complained of marked pain, in spite of sedation and administration of narcotics. Neuropsy-

## TABLE 1
## SUICIDAL ATTEMPTS PRIOR TO HOSPITALIZATION AT FORDHAM HOSPITAL

| | | | — Sex — | | | | | Stay in Hosp. | | — Disposition — | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Year | Type | No. | M | F | Age—Years | Aver. Age | Coma on Admission | Days | Aver. | Disch. Own Care | Transfer to Ment. Hosp. | Sign Out Against Advice | Died |
| 1954 | Barbiturates | 64 | 20 | 44 | 16–74 | 41.6 | 55 | 1–16 | 2.6 | 4 | 14 | 41 | 5 |
| | Miscellaneous | 21 | 11 | 10 | 18–80 | 43.2 | 11 | 1–12 | 2.6 | 8 | 5 | 8 | 0 |
| 1955 | Barbiturates | 57 | 18 | 39 | 17–84 | 40.4 | 44 | 1–11 | 2.6 | 6 | 13 | 36 | 2 |
| | Miscelaneous | 13 | 5 | 8 | 14–75 | 32.9 | 6 | 1– 6 | 2.2 | 2 | 0 | 10 | 1 |
| 1956 | Barbiturates | 34 | 4 | 30 | 15–70 | 42.9 | 16 | 1–11 | 2.5 | 2 | 12 | 19 | 1 |
| | Miscellaneous | 9 | 5 | 4 | 20–76 | 47.3 | 1 | 1– 5 | 3.0 | 2 | 2 | 4 | 1 |
| 1957 | Barbiturates | 50 | 13 | 37 | 20–84 | 48.6 | 35 | 1–11 | 2.5 | 7 | 8 | 26 | 9 |
| | Miscellaneous | 24 | 6 | 18 | 14–67 | 40.9 | 8 | 1–21 | 4.3 | 6 | 5 | 10 | 3 |
| | Total | 272 | 92 | 180 | | 42.2 | 176 | | 2.7 | 37 | 59 | 154 | 22 |

Miscellaneous: paraldehyde, Miltown, Sparine, Thorazine, aspirin, Anacin, Demerol, heroin, morphine, codeine, atropine, Benzedrine, potassium permanganate, sodium fluoride, iodine, mercurochrome, bromides, insecticides, furniture polish, cleaning fluid, rubbing alcohol, shaving lotion, gasoline, ammonia, lysol, lye, and arsenic. Ten patients had inhaled carbon monoxide. Four had lacerations.

## TABLE 2
## PATIENT DISCHARGED WITH PSYCHIATRIC DIAGNOSES FROM 1954 TO 1957 INCL.

| | | Stay in Hospital | | — Disposition — | | | |
|---|---|---|---|---|---|---|---|
| *Diagnosis* | No. | Days | Aver. | Disch. Own Care | To Mental Hospital | Sign Out Against Advice | Died |
| Acute Brain Syndrome | 241 | 1–31 | 11.3 | 109 | 64 | 37 | 31 |
| Chronic Brain Syndrome | 606 | 1–1119 | 33.1 | 84 | 458 | 23 | 41 |
| Involutional Psychotic Reaction | 43 | 1–22 | 6.5 | 3 | 33 | 7 | 0 |
| Manic Depressive Reactions | 34 | 1–21 | 14.5 | 2 | 26 | 6 | 0 |
| Schizophrenic Reactions | 48 | 1–91 | 12.0 | 1 | 35 | 12 | 0 |
| Paranoid Reactions | 17 | 1–36 | 10.4 | 1 | 13 | 2 | 1 |
| Personality Pattern Disturbance | 29 | 1–8 | 6.1 | 19 | 0 | 9 | 1 |
| Transient Situational Personality Disorders | 12 | 1–15 | 5.8 | 7 | 0 | 4 | 1 |
| Psychophysiologic Autonomic and Visceral Disorders | 31 | 1–31 | 11.6 | 27 | 0 | 4 | 0 |
| Psychoneurotic Disorders Excluding Depressive Reactions | 146 | 1–42 | 15.7 | 107 | 1 | 38 | 0 |
| Depressive Reactions | 62 | 1–15 | 4.9 | 21 | 31 | 10 | 0 |
| Total | 1269 | | 21.7 | 381 | 661 | 152 | 75 |

chiatric consultation revealed no evidence of any mental aberration or any indication that he might be suicidal. Novacaine blocks were performed on August 28, 29, 30, 31, September 3, 5, all without relief. He wanted to sign out again on his own responsibility on September 7th. On September 8, 1957, at 12:05 A.M., the nurse's aide saw the patient getting out of bed and going to a window. She rushed towards him, but the patient was already on the ledge, and when she grasped him, he struck her on the jaw, and she lost her grip on him. He jumped three stories, sustaining multiple fractures, contusion and abrasions. On his return to the ward he was confused and disoriented. Upon consultation with the visiting neuropsychiatrist and orthopedist, he was transferred to Bellevue Psychiatric Hospital on September 9th. Although this patient had an initial neuropsychiatric examination, the neuropsychiatrist found no evindence of mental aberrations, and the patient was considered an organic problem in relation to his sciatic syndrome.

These three cases showed no evidence of suicidal intent, mental aberration or emotional instability, prior to their suicidal attempt.

Although our study is detailed from 1954 to 1957, on review of the records we have found no evidence of any suicidal attempt at Fordham Hospital from 1951 until 1956. It is to be emphasized that for the years 1951 through 1953 there were 143 patients who were admitted to Fordham Hospital as a result of attempting suicide prior to admission. During the same period there were 844 patients discharged with psychiatric diagnoses.

*Discussion*

When patients are admitted to a municipal general hospital, it cannot be ascertained who are suicidal unless suicidal attempt has been made. It is impractical to take a psychiatric history of every patient admitted to a general hospital. Even if this were done, there is no definite criteria to foretell which patient would attempt suicide. Psychiatric patients are not admitted to the general wards of a hospital as it is still believed that these patients are more prone to suicide. In mental hospitals precautions are taken for persons who have attempted suicide or appear suicidal. There is no evidence to prove that if these psychiatric patients were handled in a routine manner, similar to the open ward psychiatric patient, or to the ordinary patient, that they would be more prone to suicide. Wilmer,[10] during a ten month period, observed 939 male psychiatric patients, naval personnel, admitted for ten days to a general psychiatric ward which he called the psychotherapeutic community. On admission many of these patients were disturbed and quite a number were suicidal, but his policy was to consider all patients as not dangerous. The seclusion room and restraints were not necessary and sedatives were rarely employed. Emphasis was on social factors of tranquilization rather than chemical tranquilizers. No suicide was reported in this series of patients. Moll, in the discussion of Ozarin's[11] paper concerning architectural structure in relation to space in general hospital psychiatric wards, states that in the psychiatric department of the Montreal General Hospital, "we have no locked doors nor even security screens on our windows and yet the department is situated on the fourth floor. All windows can be opened and the patients are allowed complete freedom to circulate wherever they may wish, even though some of them are actually disturbed, severely depressed or entertaining suicidal intent."

In 1792 Pinel liberated the mental patients from chains. However, except for a few mental hospitals, the suicidal patients are still kept under close observation and maximum security, isolated from the remainder of the medical community. Psychiatric units have been established in the general hospital, but they function separate and apart from the general hospital. Only recently has there been a movement to have psychiatric patients an integral part of general hospitals. At the end of World War II there were 176 general hospitals that admitted mental patients. According to the latest statistics, Bush[12] reports that as of January 1958 there are 584 general hospitals that admit mental patients, and 223 of these hospitals place the psychiatric patients in regular medical or surgical wards.

If a patient manifests an obvious psychiatric diagnosis he is not admitted to Fordham Hospital, the municipal general hospital, but sent to a local municipal psychiatric hospital. Therefore, it may be said that the cases admitted to Fordham Hospital are selected. Nevertheless, 1,269 patients with psychiatric diagnoses were discharged from Fordham

Hospital in a four year period without any suicidal attempt during their hospital stay. Many, not classified as psychiatric patients, were querulous and irritable, requiring a psychiatric consultation. They were more difficult to manage from an administrative standpoint, than the psychotic or psychoneurotic patient.

*Summary and Conclusion*

1. Of a total of 37,860 patients admitted during the years 1954 through 1957 to Fordham Hospital, a municipal general hospital, 272 cases were admitted after a serious suicidal attempt. In the same period 1,269 cases were discharged with a psychiatric diagnosis.

2. The three patients who attempted suicide during the years 1956 and 1957, one unsuccessfully, were not psychiatric patients. The three attempts were made by jumping through a window.

3. Patients who attempted suicide, prior to admission, and those with psychiatric diagnoses, among whom were obviously many potential suicides, were not segregated in any special ward, but mingled freely with the general hospital population.

4. Patients who attempted suicide, prior to admission, did not repeat the attempt while in the hospital.

5. Patients with psychiatric diagnoses did not attempt suicide during their hospital stay.

6. In annual reports, the number of suicidal attempts, successful or unsuccessful, should be recorded.

7. The Standard Nomenclature of Diseases and Operation should include a category for suicide or attempted suicide.

8. The authors believe that patients who attempt suicide prior to hospitalization and those with psychiatric diagnoses can be kept and treated on a general medical and surgical ward for periods up to thirty days, without fear of suicide or of disturbance to other patients.

9. There is no need of any change in the suicidal precautions which are employed routinely on general medical and surgical wards.

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## Discussion of Suicidal Risk

DR. LOUIS WENDER, N. Y.

Whether general hospitals should accept mental patients or borderline cases, that talk of suicide or have attempted suicide, has long been a moot question. From the psychiatric viewpoint there is agreement that the risk in accepting these patients is minimum. However, there is a medico-legal aspect that the hospital may become involved in legal complications. While in municipal hospitals the superintendent and physicians may not be held responsible, a suicidal attempt or a successful suicide in a voluntary or private hospital may give rise to a cause of action against the hospital and the people who operate the hospital. Therefore, this problem cannot be solved just with statistics. It is the responsibility of the community to educate the public in order to avoid medico-legal complications.

This statistical study should have included a study of the personality of the individuals and the psychiatric problems of the patients at the time of their suicidal attempt. After all, the common denominator among the patients admitted after a suicide attempt is one symptom—self-destruction and in a short discussion it would be impossible to discuss what impels people to suicide. There is a measure of agreement among those who stress so-

ciological factors and those who stress psychiatric factors, and although the concepts are formulated differently, there is general agreement that the personality factors are paramount.

From a psychodynamic standpoint, we have the theory of the death drive and the life drive, which are in constant conflict. Therefore it is possible that in a period of frustration, too intense for an individual to endure, the death drive takes the upper hand and the result is an impulsive suicidal attempt. This corresponds to the theory of the conflict of love and hate. We must also consider the hysterical or infantile person who attempts suicide to gain advantage or punish the environment. Most of the time such people make half-hearted attempts. If they succeed, it is just by accident. We are all aware of fantasies that children elaborate on when they talk of death, how they are lying in their coffin, and how the family will weep. This mechanism is later elaborated in older life by suicide. These suicides are actually not hostility directed against one individual, but rather against the whole family constellation. We must recognize, however, that no individual can really conceive of himself as ceasing to exist. Religions deny death and translate this denial into concepts of man's immortality. Consciously we realize the inevitability of death but unconsciously we do not accept it.

Successfully carried out suicide is a fairly common occurrence in patients suffering from chronic physical ailments admitted to a general hospital. The act is not as frequent in a hospital for chronic diseases. People with chronic ailments face a total frustration. Their depression is not superficial; it is a deep ego loss. They cannot accept the illness with its dependency, while watching others in the general hospital improve, and apparently the wish to die is superimposed upon the wish to live. In a sense, they embrace death before death embraces them. Incidentally, as reported by Dr. Friedman, these suicides occurred late at night or very early in the morning. They just cannot face the next day, which is full of life for everyone except for them.

The question arises: Can a general hospital reduce the suicide rate even further? This question does not appear cogent because the present statistics are low, and it would not be possible to lock all doors and windows and practically restrain patients with chronic illnesses or patients admitted for suicidal attempt. It is a well known fact that a patient who makes one suicidal attempt waits some time before making another. Very seldom will a patient, admitted for attempted suicide, make another attempt immediately. Whether this depends on the amount of guilt and punishment the patient has in his own conscience, can only be evaluated by a study of the case history and examination of the patient. My experience is that there are very few recurrent suicidal attempts within a short period. Those who do are either very confused or markedly perplexed, and their reasoning and judgment completely impaired. Their behavior is compulsive and such patients can be diagnosed very easily. Usually the suicidal patient, after his first unsuccessful attempt thinks twice before trying again.

The study Drs. Friedman and Cancelleri have presented is a valuable contribution. The only suggestion that I would advance is that these patients should be kept in the hospital longer, if necessary against their will, and that a psychiatric and social history be obtained so as to be able to give the family an idea of the cause and recommended therapy.

*Mr. John J. Ritter:* In my experience at Fordham Hospital from January 1947 to the present date, there were only eight cases of attempted suicide by patients on the wards. All were attempted by jumping from windows. Five ended in death. Three patients recovered and were subsequently sent to Bellevue.

The windows in our hospital are of the double hung sash type, with wire mesh screening on the outside, which is no protection against jumpers.

It is my opinion that with sufficient trained professional personnel and the use of a type of window which does not permit passage by a body, most psychotic cases could be taken care of in an open ward. However, professional groups and the general public would require much education to change their traditional thinking as to these patients.

The greatest problem is the nuisance that the psychotic patient creates on the wards. He takes up excessive time and effort of overworked, understaffed ward personnel and he is not readily accepted by the other patients on the ward.

Statistically, a record of eight attempts at suicide in a total of approximately 135,000 admissions to a general hospital is a ratio of 1:16,875 admissions, and speaks for itself.

(Mr. Ritter is Assistant Hospital Administrator at Fordham Hospital, and therefore speaks with a great deal of experience about hospital management.)

*Dr. Emerick Friedman:* About the psychotics causing difficulty on the ward, I believe that since the introduction of the tranquillizers we have kept this to a minimum at Fordham Hospital. Our only real difficulty is with alcoholics.

*Dr. Morton Hand:* I would like to cite our experience with chronically disabled patients in a hospital with a census of 800. These people remain for years. They are for the most part orthopedically or neurologically disabled patients, and we have on the average three to five attempted suicides a year, approximately three to four that are successful.

Of more importance than the fact that we have a few suicides is the fact that each time a suicide occurs other patients in the ward become inquisitive as to whether or not there was difficulty in accomplishing the act, and they often openly express their own desire to enter into a similar form of activity if they but had the courage and were sure that they would succeed.

# Psychomotor Paroxysms of Non-Epileptic Origin

EUGENE REVITCH, M.D.

Paroxysmal outbursts of disorganized behavior with or without hypermotility, autonomic manifestations, falling down and various degrees of alterations of consciousness frequently present a difficult problem in the differential diagnosis between epileptic and non-epileptic disorders. In accordance with the Jacksonian concept we now believe that the clinical manifestations of epilepsy are correlates of an excessive neuronal discharge in the brain. Unfortunately scalp electroencephalography is not always a reliable diagnostic tool since paroxysmal tracings may be found in non-epileptics, while perfectly normal records are not uncommon in epileptics. Furthermore, the very boundaries of epilepsy are not clear in spite of tremendous advances in the field. Thus for instance Schwade and Geiger[1] recently challenged the very concept of thalamic and hypothalamic epilepsy described by Gibbs and Gibbs.[2] According to the authors, the 6 and 14 per second spikes described in this condition are connected not with epileptic phenomena, but with thalamic, hypothalamic and amygdalic impulses released by an emotional trigger.

H. Baruk and his school in France believe that in addition to hysterical attacks there is a whole spectrum of paroxysms extending from quasi voluntary events to epileptic manifestations. The French authors have described these seizures under the name of "crises neuropathiques" and "crises catathymiques."[3,4] The views of the French authors seem to revive the old concept of Gowers[5] who questioned existence of intermediate forms between hysteria and epilepsy.

For a period of over three years the author paid special attention to patients with paroxysmal psychic, motor and autonomic phenomena which at some time were thought to be of epileptic origin and frequently treated as such with anticonvulsive medication. The clinical material was collected among inmates of the New Jersey prisons, among the cases referred to the New Jersey State Diagnostic Center by courts and agencies, and among patients with similar episodes seen in private practice. The institutional patients were particularly valuable since it was possible to observe them for two to three years and some of them were followed indirectly for a period of five years. This study, as well as a review of literature, clearly indicated a spectrum of conditions with various degrees of dominance of physiological and psychological factors in the causation of the seizures. It is possible to divide the attacks into four large and somewhat heterogeneous groups:

I. Physiological factors such as hypoglycemic reactions, syncopes, etc.

II. Attacks due to physiological and psychological factors with physiological dominance; these seizures are connected with physiological immaturity of the nervous tissue or to brain lesions. Due to this, emotionally triggered impulses cannot be coordinated into purposeful activity or inhibited. This is common in childhood encephalopathies, in childhood schizophrenia and in impulsive behavior connected with 6 and 14 per second positive spikes and in the aggressive psychopaths with theta activity in the mid-temporal region as described by D. Hill.[6]

III. Physiological and psychological factors with psychological dominance: To this group belong outbursts of uncontrollable anxiety with behavioral disorganization, outbursts of anger and excitement occasionally with breath-holding spells in paranoid personalities.

IV. Due to psychological factors: To this group belong purely psychogenic conditions such as hysterical dissociations and simulation.

Most of the seizures observed by the author belonged to Group II and III. In Group II the most outstanding cause of diagnostic error were cases of childhood schizophrenia with various impulsive manifestations and blind rages. A thorough history taking usually revealed specific factors producing what would seem to be a psychomotor seizure. For instance, a three year old boy had attacks of uncontrollable rage with falling down on the floor in specific situations such as men and women appearing together on television, his mother reading a newspaper, etc.

The Group III was predominantly prevalent among prison inmates of the younger age groups. The seizures consisted in what seemed to be unprovoked rages with altera-

From New Jersey State Diagnostic Center, Menlo Park, N. J.

tions of consciousness, assault, destruction of objects, self-destructiveness as well as falling down or with disorganized, purposeless motility. These attacks seemed so out of context that the patients received anti-convulsive medication prior to the re-evaluation of their condition. It appeared that practically all the subjects presenting these phenomena were of a paranoid personality structure with a suspicious, distrustful and hostile orientation to the human environment. At the New Jersey Reformatory for Women, 15 inmates with psychomotor outbursts were all classified as paranoid personality, while out of 20 inmates without psychomotor outbursts and taken at random for this study, only four were classified as such. As a general rule, attacks in this group disappeared with emotional maturation, better motivation and supportive relationship with a member of the staff. EEG's were abnormal only in four out 15 patients at the Reformatory for Women, were of borderline quality in a few other cases in the younger age group and normal in the majority of patients.

Many of the patients in describing the seizures brought up the subjective experience of bitemporal, throbbing headache and difficulty in breathing prior to the blackout. Hypnosis, sodium amytal interviews and repeated psychiatric examinations for a long period of time usually discovered precipitating incidents causing frustration and anger. Thus a 28 year old woman with a paranoid personality structure, who in adolescence was considered to have epileptic equivalents described the attacks in youth as follows: "I was depressed. I wanted to be with my mother. Nothing mattered. I was upset. It was mostly nerves but now I can control my temper." An inmate in a male prison presented attacks of falling down with loss of consciousness as well as outbursts of blind rage with assaultiveness. These attacks were provoked by quasi-delusional impressions that someone was going to hurt him. On a few occasions he found himself in strange places, not knowing how he got there. On several occasions when given sodium amytal intravenously he became delirious, delusional and dangerously assaultive. With change of environment and assignment to a shop with a sympathetic supervisor, the attacks disappeared in spite of removal of anti-convulsive medication. He had another attack, however, two years later when confronted with an unsympathetic officer who, he felt, wanted to harm him. In the history of some individuals belonging to Group II, occasional convulsive attacks can be elicited in the history. The case of a thirteen year old boy who had been followed for two years is a good example. He apparently had a convulsive seizure early in the morning at the age of eight and then at the age of ten years. Repeated EEG's since the age of eight years revealed theta activity in the left temporal area. He was on anti-convulsive medication between the ages of ten and thirteen years at which time for a period of three weeks he was tense, nervous, with attacks of flushing of the face, unprovoked assaults on his foster father and on his dog. Increase of anti-convulsive medication did not modify the pattern. During these three weeks he was subject to severe emotional stress, since his mother planned to remove him from the foster parents whom he considered as his real parents. With change of the stressful situation, the attacks disappeared and he has been free of any seizures for the past year in spite of the fact that anti-convulsive medication had been withdrawn. The history of this boy and other similar cases bring forth the following hypothesis. A high threshold with epileptogenic focus may occasionally show up under strong stimuli. At the same time the damaged area in the brain weakens the ability of of the central nervous system to redirect or inhibit emotionally triggered release phenomena. This may also explain Gower's assumption that some hysteroid seizures may later become real epileptic attacks.

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## Discussion of Paper by Dr. Revitch

HANS STRAUSS, M.D.

Dr. Revitch has presented much case material with a great variety of syndromes. He mentions for example hysterical dissociation, rage reactions, autonomic and psychic paroxysms. He also described akinetic seizures and breathholding spells without, however, adhering to the exact meaning which these words have in neuropsychiatric usage.

The characteristic common to all in Dr. Revitch's group is evidently the occurrence of short, episodic alterations of behavior which in all his cases appear on the background of less obvious chronic psychiatric difficulties. On the basis of these episodic disturbances Dr. Revitch speaks of psychomotor paroxysms. He does not use the expressions psychomotor attack or psychomotor seizure. However, it seems to me that paroxysm, seizure or attack signify essentially the same reaction and, therefore, as far as I can see, these patients do not suffer from what is generally called a psychomotor attack or seizure or paroxysm. The term psychomotor seizure, as it is now employed, following Gibbs and Lennox, is not well chosen for it denotes mainly those states which psychiatrists previously used to call twilight states or dreamy states. While I do not deny that such twilight states can occur outside the field of epilepsy, I do not see that the observations, made by Dr. Revitch, should be diagnosed as such states. Many of them show evidently an emotionally induced narrowing of consciousness but no general depression of the level of consciousness. The word "psychomotor" should not be used to describe the conditions discussed by Dr. Revitch for this will inevitably lead to confusion and contribute nothing to the necessary clarification.

Is there any relationship between these cases and epilepsy? Of course one will think of such a relationship in view of the episodic appearance of the disturbances. Many observations have been made, beginning with those of my teacher Kleist in 1926 up to those by Weil, Heath and Epstein, which have shown the importance of epileptic mechanisms in some rather complicated episodic psychotic states. Dr. Revitch denies a relationship of his observations to epilepsy on the basis of clinical and electroencephalographic studies. In most cases the EEG was normal, at least as long as no special provocative methods were used. In two cases Dr. Revitch describes bursts of slow activity. Of course this is an unspecific type of abnormality which is seen quite often in epilepsy but also in many other conditions.

However, the presence of this abnormality in these cases shows that they have a disturbance in cerebral activity which can be defined physiologically. This is, in my opinion, of the greatest importance. We should try in every psychiatric case to discover by all available means whether there is a disturbance of brain function which we can define in terms of brain physiology. Once we have found such a disturbance, the problem arises what is its role in the pathogenesis of the deviation in behavior. Are the psychiatric manifestations direct and simple, one might say obligatory, sequelae of the disturbed brain function as e.g. the appearance of photopsias with an irritative process in the optic system? If they are such obligatory sequelae they will occur in every person with the same physiological disturbance of brain function, independent of personality make-up or the present situation. The relationship of the behavioral disorder to the disturbance in brain physiology may, however, be much more complicated. The abnormal cerebral activity may result primarily only in a slight diffuse disturbance of cerebral function. This disturbance, however, may make it impossible for the patient to cope with difficulties in the same way as a person without such a disturbance and so lead to abnormal reactions whose type is determined by many factors including the personality of the patient, the present setting and others. In this respect let me point out that probably quite a few of Dr. Revitch's patients suffered from some disturbance in cerebral physiology, even if their EEG was normal. Many of them had low IQ's pointing to some form of cerebral impairment.

I fully agree with the statement that there are patients with episodic outbursts of abnormal behavior in whom no disturbance of brain physiology can be demonstrated by any means available now. Dr. Revitch would not have written this paper if he had not been fully aware of the fact that such a disturbance can be shown in others. Its demonstration is of theoretical and even practical importance. I refer here as an example only to those children with behavior disorders and those psychopathic personalities who show bursts of slow activity in their EEG and who can frequently be helped greatly by simple drug treatment.

While I have to disagree with many of Dr. Revitch's formulations, I feel that his paper is important because it brings up the problem of physiologically definable disturbances of brain activity in psychiatric disorders.

It is very gratifying to see in the last years how biological and physiological research begins to play an increasingly greater role in psychiatry. I am fully convinced that with the use of this approach and with the aid of new tools of research, e.g. depth recording from the brain, we will in the not too distant future discover basic deviations of the brain from its normal physiological activity in conditions where such deviations were not even suspected before.

*Dr. Leo Alexander:* This is medically and legally a most important area, because in court cases these questions often arise and those who have read Dr. Lindesay Neustatter's book "The Mind of the Murdered," *Christopher Johnson,* London, 1957, may recall this. He also included a cause celebré that we struggled with in Boston. Finally Dr. Wm. G. Lennox was brought in as arbiter. In this case a boy had killed his favorite aunt in a brutal attack, and

the late Mr. Ogilvie called as technical consultant to the prison at my suggestion produced magnificent records of left temporal spikes. The boy had suffered a head injury, and his first convulsive seizure at age 2, a second seizure and a fall down a flight of stairs at age 11. There were outbursts of brutal assaultiveness against playmates and siblings; once after an argument he put a plate of hot beans over the head of his brother, scalding him very severely. There were similar outbursts on three occasions with dysmnestic fugue states of varying duration while serving with the Marines, and the final brutal attack on the aunt. He had abnormal reflexes on the right, implicating the left pyramidal centers and a definite left temporal lobe focus with spikes. I testified to that effect, but I was contradicted by a very venerable psychiatric expert, who stated that the EEG can never have any bearing on the mental state. He said he had seen many epileptics with very abnormal EEG's and yet were normal mentally and seen brutal acts committed by people with normal EEG's. He claimed the abnormal EEG had no bearing at all.

I then testified that the temporal lobe focus, in view of Gibbs' findings, has a certain specificity. Nevertheless the jury convicted him because the venerable expert was more persuasive than my too scientific, too theoretical testimony. Then a commission was appointed on which were epileptologists who confirmed my findings, did more electroencephalograms and the boy's sentence was commuted.

When Lindesay Neustatter came to Boston, I turned all the data over to him, which he included in his book. He reported some very interesting cases.

From a medico-legal point of view this problem is very important. Because the person is an epileptic there is a much stronger case.

Dennis Hill and William Sargant contributed an interesting case of matricide. This man killed his mother during the height of an argument in what appeared to be a psychomotor fit, facilitated by hyperventilation and hypoglycemia. The jury found him not guilty because of insanity.

Dr. Revitch's great contribution is that he has brought to us clinical material that we rarely see except when brought into court. He sees it in pure culture in prison practice. The entire psychiatry of the criminal is virgin territory, never actually studied on a wide scale. I hope Dr. Revitch will make a systematic study because very little is really known about the subject.

In the Army we saw many of this type. We saw many more of the things which you find rarely in civilian life. I don't know whether it is the pressure of Army life, the confinement or what it is. The British made some statistical studies of the subject. More of those crimes occurred in cold weather than in hot weather. They thought that brain hydration had something to do with it.

*Dr. Joachim Luwisch:* I am inclined to agree with Dr. Straus. From Dr. Revitch's presentation I am not convinced that those cases did not have epilepsy or a disorder which we call convulsive disorder.

I would like to ask Dr. Revitch, a) did he try medications with those patients and did he see any change in their behavior, and b) does he or did he take into consideration the fact that in about 5 per cent of proven epileptic cases the EEG is normal?

*Dr. Leo Alexander:* I agree with Dr. Luwisch that perhaps sleep recordings may be in order in view of Gibbs' work.

*Dr. Emerick Friedman:* I would like to mention a classification of epileptic personality, somewhat in the discard at present, which contains references to phenomena that were described, namely, that various types of emotional outbursts can occur without definite EEG findings at the time or, let us say, that EEG's were not taken at the time of the events.

I have now several cases referred by the New York State Rehabilitation Department which has become interested in long term disabilities in which certain phases of epilepsy have played a prominent role. Several instances have come up recently in which the patients had definite diagnosis of epilepsy and everyone who had seen these patients classified them as epileptic states.

In discussions with these patients it was noted, between the attacks, the patient recognized and everybody around recognized, numerous outbursts of psychopathological phenomena, in some instances criminal psychopathology. No one took an EEG at the time. The patients were neither hysterical or epileptic presumably at that particular time. Is such a phenomenon of personality or of some other mechanism, some as yet undetermined type of electrophysiologic episode?

*Dr. William Holt, Jr.:* To me the point of Dr. Revitch's paper is not that he had some people with epileptic EEG's and some with convulsions but that he was dealing with a group in whom there often was found conscious awareness of their behavior during emotional outbursts or the outbursts of disordered behavior. In this respect he considered them different than the classical hysterical patient and quite different from the classical epileptic patient. He saw that these were people who had unstable emotional make-up, with a tendency to get into antisocial activity and, of course, appeared primarily in prison populations.

I, also, see such patients occasionally and I think that Dr. Revitch has performed a useful service in pointing up the fact that though there is some similarity between the epileptic and hysteric in these groups, in many instances they are neither one nor the other. I think it would be well to exclude those that have definite epileptic histories or hysterical episodes so that we can focus more definitely on this intermediate group who very often are antagonistic and suspicious of people in general, especially authoritative figures.

*Dr. Leo Alexander:* Dr. Holt has made a very

important point and I would like to ask Dr. Revitch whether he has seen in his prison population any attempted suicides by impulsive individuals, by strangulation, which Stern has described, where there is always a stereotyped tendency to put on or have on their person female clothing. There are numerous diseases in criminals and social deviants that we have not sufficiently studied.

*Dr. Martin Hand:* The term "epilepsy" is more or less of a cliché that we use in referring to a type of apparent motor phenomenon. On the other hand, we also are aware of the fact that some disturbances in cerebral physiology can be manifested in other non-motor forms. The cases Dr. Revitch has discussed are chiefly behavioral disturbances. In electroshock therapy following treatment we frequently encounter behavioral disturbances that can not be easily distinguished from those that occur spontaneously in the syndrome that is called psychomotor epilepsy. Yet occasionally we see patients in treatment who are assumed to be mentally disturbed but who in the midst of a rather continuous mental disturbance manifest paroxysms of behavioral which cannot be truly differentiated from the so-called psychomotor epilepsy. If one does an EEG on such a patient dysrhythmias will be found sometimes with focal alterations in the temporal lobes.

My thought in the matter has been that some of these patients may represent a form of psychomotor epileptic status. Some of these patients when treated with electric stimulation will tend to normalize their behavior after a period of time. I have on record one patient who after recovery showed a normal tracing.

The fact that in most instances the electro-encephalogram on psychotic patients shows little or nothing, should not preclude considering that some of them may be epileptics. The point that I wish to make is that even in motor epilepsy there is a percentage of individuals who show no abnormalities in the electro-encephalogram after various forms of stimulation.

If we were to weed out of the psychotics that we encounter, those patients with paroxysmal behavioral disturbances that seem to be occurring in the course of a more chronic type of mental disturbance, we might more frequently find patients that may be considered epileptic.

*Dr. Eugene Revitch:* As to the objection to calling these attacks psychomotor paroxysms, I must admit that I could not find another suitable word to describe them. I would like to stress that many of the patients with these attacks were originally diagnosed as cases of psychomotor epilepsy. To the second question of whether I used activation methods in the electroencephalograms, the answer is that unfortunately this was not possible since the records were taken in various state laboratories and by various technicians. I believe that, as a general rule, thorough history taking clinical studies surpass electroencephalography in importance. For instance, the EEG of one of the patients showed slow bursts coupled with fast activity. Because of the record she was diagnosed as a case of epilepsy. Yet under hypnosis and sodium amytal it was possible to determine the psychogenic nature of her fits.

As to whether I tried to control the seizures with anti-convulsive medication, the answer is that I actually took these patients off Dilantin and obtained freedom from attacks by placing them in a different cottage or with different supervisors. Mr. Weiss, the psychologist from New Jersey Prison Farms, assisted me in a clinical follow-up of a prisoner with this type of seizure. This prisoner improved after withdrawal of Dilantin just by placing him with a different supervisor.

To the question about suicide-strangulation among prison inmates, I must answer that I have not seen it so far. I would like to stress, however, the frequent occurrence of self-destructive tendencies which reminds me of two historical examples: Alexander the Great and Vincent VanGogh. Alexander the Great is described by Plutarch as a suspicious, paranoid personality. Not unlike the cases I had the opportunity to observe, he developed a fit of fury against his friend Clytus, whom he pierced with a spear. Immediately afterwards he attempted to stab himself. The fit was connected with an outburst of paranoid ideation. VanGogh's fits were also outbursts of fury, stimulated by flashes of paranoid thinking. Casces of this sort cannot be diagnosed as psychomotor epilepsy and should be isolated as separate entities. The first two cases presented here did present occasional epileptic attacks, yet most of these seizures were not epileptic but emotionally triggered release phenomena connected with physiological and psychological immaturity coupled with inability to inhibit strong impulses. The first case with a true temporal spike improved not with medication but with Reiter's electrostimulation.

# *Diseases of the Nervous System*

## INDEX 1958 — Volume XIX


**Abreaction Produced by Low Non-Convulsive Electrostimulation** ..... Supp. July 87
Paul H. Wilcox

**Acetylcarbromal and Bromisovalum in Combination** ..... February 73
Theodore M. Feinblatt, Henry M. Feinblatt and Edgar A. Ferguson

**Adaptation and Maladaptation—Contingency Theory** ..... August 343
John R. Whittier

**Anesthetist in Electroshock Therapy** ..... Supp. July 41

**Apparatus and Method for the Study of Conditional Reflexes in Man (An Abstract)** November 495
Leo Alexander

**Atherosclerosis—Resistance to Development** ..... May 207
Michael J. Carver, Clarence A. McWhorter, Herbert P. Jacobi and Jackson A. Smith

**Behavior Genetics and Differential Psychology** ..... Supp. July 17
Jerry Hirsch

**Benactyzine—A New Antiphobic Agent** ..... September 394
Theodore M. Feinblatt, Henry M. Feinblatt and Edgar A. Ferguson, Jr.

**Brain Measurements Electronically Determined** ..... October 449
Alfred E. Eyres, Reuben Reiter and Josephine Knight

**Brain Tumor Presenting As Convulsive Disorder** ..... December 518
Robert R. J. Strobos, Eben Alexander, Jr., and Richard L. Masland

**Carbon Dioxide-Electroshock Combination** ..... April 155
Robert A. Richards

**Childhood Schizophrenia: A Review** ..... June 253
Jay Kuten and Sandra L. Kuten

**Chlorpromazine and Dextro-Amphetamine on Severely Depressed Patients** ..... June 249
Eugene Davidoff

**Chlorpromazine Effects on the Blood Pressure Following Mecholyl** ..... May 216
George A. Bray and Daniel H. Funkenstein

**Chlorpromazine in Treatment of Chronic Schizophrenia** ..... January 20
Julian Abrams

**Chlorpromazine—Results on Chronically Nude, Incontinent, Combative Patients** .... August 339
Werner Tuteur, Rochus Stiller and Jacob Glotzer

**Chlorpromazine Sustained-Release—Use on Hospitalized Chronic Psychotic** ..... April 173
John Vasconcellos and Albert A. Kurland

**Cigarette Neurotics** ..... July 305
Edmund Bergler

**$CO_2$ Therapy—Failures With** ..... May 209
John D. Moriarty

**Cogito, Ergo Sum: Discussion of Perception, Mind, and Brain** ..... November 480
N. L. Mason-Browne

**Communication in Stuttering** ..... April 178
Dominick A. Barbara

**Compazine (High Dosage) in Chronic Schizophrenia** ..... July 309
W. T. Holman

**Defense Mechanism of "Fading News Value of the Intolerable"** ..... April 164
Edmund Bergler

**Drawing Completion Test** ..... May 223
F. De Cori

**Effect of a Cholesterol Lowering Agent on the Aged Mentally Ill** ..... December 511
Michael J. Carver, Joseph P. Dailey, Robert L. Colescott and Jackson A. Smith

**Ego Functioning As Reflected in Skin Temperature Change** ..... September 388
Stanley S. Kanter, Alberto DiMascio and Peter D. Watson

**Electric Stimulation of the Diencephalon** ..... Supp. July 80
Carl Breitner
October 439

**Elipten$^R$—A New Anticonvulsant** ..... August 349
Vasilios S. Lambros

**Electroshock and Drugs—Combination in Chronic Psychotic Patients** ..... April 161
Milton Kramer and Douglas Goldman

**Electroshock Process—Experimental Studies** ..... March 113
Max Fink, Robert L. Kahn and Martin A. Green

**Electroshock Therapy in the Presence of Retinal Detachment** ..... September 401
William Karliner

**Electro-Sleep in a Chronic Disturbed Service** ..... Supp. July 84
Maurice Fenichel

**EST Induced Fractures—Reduction With Pentothal-Succinylcholine Anesthesia** .... September 385
H. I. Newbold

**Establishing a New Psychiatric Department Within a Medical School** ..... August 327
Elmer L. Caveny and James N. Sussex

**Etiologies of the Schizophrenic Syndrome** ..... March 108
David A. Freedman
**Experimental Investigations** ..... Supp. July 54
**Factors Influencing Academic Achievement** ..... March 97
F. J. Ryan and W. G. Scanlon
**Factors in Patients' Failure to Return to Clinic** ..... October 429
James M. A. Weiss and K. Warner Schaie
**Frenquel Evaluation in Treatment of Psychotic Veterans** ..... August 345
Roy M. Barber
**Friedreich's Ataxia Ascribed to Trauma** ..... January 35
Jacob H. Friedman and Alberto Arengo
**Frontal Leucotomy and Its Congeners** ..... January 11
Walter Freeman
**Funkenstein Test—Effect of Drugs on** ..... August 352
Frederick B. Charatan
**Genetics of Mental Deficiency** ..... Supp. July 31
Gordon Allen
**Glucagon in Terminating Insulin Coma** ..... November 485
Augusto J. Esquibel, Albert A. Kurland and Daniel Mendelsohn
**Glucose Insulin Tolerance Test and Insulin Coma Therapy** ..... July 299
Margaret R. Read and James S. Kaufman
**Hereditary Defects in Protein Synthesis As Related to Psychiatry** ..... Supp. July 25
I. Herbert Scheinberg
**Hexobarbital Sodium in Clinical EEG** ..... July 297
Herbert C. Merrillat, Paul T. Cash and Martin J. Krakauer
**Hodgkin's Disease—Cranial Neuropathy in** ..... June 260
Roger Merritt Morrell
**Hydroxyzine in Neuropsychiatric States** ..... May 220
Leon M. Simms
**Incontinence on a Closed Ward** ..... January 15
J. L. Cameron and Betty Griggs
**Interpersonal Theory and Intensive Psychotherapy Procedure** ..... October 417
Eugene C. McDanald, Jr.
**Iproniazid in Orthopedics** ..... December 546
David Bosworth
**Iproniazid in Psychotherapy—Adjunctive Use of** ..... April 182
Frank Orland and Nathan L. Comer
**Iproniazid in Pulmonary Tuberculosis** ..... December 545
George G. Ornstein
**Laryngospasm: Incidence and Management in Electroconvulsive Treatment** ..... February 61
Ernest J. Fogel and K. H. Hinderer
**Lobotomy in Childhood** ..... May 201
H. C. Holland, E. G. Newman and L. B. Hohman
**Marsilid—A Dangerous Drug?: Discussion** ..... December 548
**Marsilid and Other Amine Oxidase Inhibitors—Toxicology of** ..... December 539
Lowell O. Randal and Robert E. Bagdon
**Marsilid in Psychotic Depressed Patients—A Study** ..... November 491
Antonia J. DeFeliz Ferreira and Harry Freeman
**Marsilid Toxicity** ..... December 541
Robert J. Floody, Robert E. Dixon and V. D. Mattia, Jr.
**Measuring Indirect Effects of Treatment on Chronic Wards** ..... April 167
A. F. Mœszaros and D. L. Gallagher
**Meprobamate—Effect on Patients in Intensive Psychotherapy** ..... November 497
Alan A. Lipton
**Military Psychiatry—The Basis of Effective** ..... July 283
Eric Bell, Jr.
**Modified and Unmodified Electroshock Treatment—A Study** ..... January 29
Leston L. Havens
**Monopolar Electrocerebral Therapy** ..... October 447
Joseph Epstein
**Multipolar Electrocoma Therapy** ..... Supp. July 83
Emerick Friedman ..... October 445
**Music—Influence Upon Verbal Participation in Group Psychotherapy** ..... February 66
Leo Shatin and Carl Zimet
**Myoneural Blockade in Psychiatric Electrotherapy** ..... Supp. July 71
Lawrence H. Gahagan and D. Jeanne Richardson
**Narco-Stimulation** ..... December 534
Albert A. LaVerne
**Nasal Airway for ECT** ..... August 353
Joseph Epstein
**Newer Psychiatric Drugs** ..... Supp. July 47

**Niacin—Effect on the Electroencephalogram** ..... March 100
P. O. O'Reilly and R. P. Keogh

**Non-Convulsive Electro-Cerebral Stimulative Therapy** ..... October 437
Paul H. Wilcox

**Non-Convulsive Technics—Value of** ..... Supp. July 64

**Peripheral Electrical Stimulation** ..... October 443
Charles H. Jones and James G. Shanklin

**Perphenazine in 100 Hospitalized Patients** ..... October 428
Harry F. Darling

**Prochlorperazine and a Prochlorperazine-Combination in Disturbed Patients** ..... December 531
Roy C. Noble and Charles W. Castner

**Prochlorperazine in Hospitalized and Private Psychiatric Patients** ..... March 118
Frank Wilcox

**Promazine, Intravenous—Effect on Arousal Responses in Man** ..... July 307
W. P. Wilson and James S. Glotfelty

**Psychiatric Aspects of Multiple Sclerosis** ..... February 77
Alfred Gallineck and Lothar B. Kalinowsky

**Psychiatrist's Responsibilities** ..... August 332
Samuel Liebman, Milton A. Dushkin, Marc Nissenson and Marvin Schwarz

**Psychoanalytic Applications to Levels of Group Psychotherapy With Adults** ..... September 379
Benjamin Kotkov

**Psychodynamic Drugs** ..... June 265
Richard C. Proctor

**Psychodynamics of Filicide and Matricide** ..... November 475
Edward Podolsky

**Psychogenetic twin data—An Appraisal of** ..... Supp. July 9
Franz J. Kallmann

**Psychomotor Epilepsy—Symbolic Language Discrimination in** ..... November 469
Alice Calvert Roberts

**Psychomotor Paroxysms of Non-Epileptic Origin** ..... December 562
Eugene Revitch

**Psychotherapy—Factors Affecting Results** ..... July 289
Jerome D. Oremland, Don D. Jackson, George Krieger and Robert Blazejack

**Rauwolfia Alkaloids—Effect on Chromatophores I** ..... February 53
William J. Turner

**Recovery from Insulin Coma and Hematoencephalic Exchange** ..... March 104
Williamina A. Himwich and JoAnn C. Petersen

**Reserpine-Methylphenidate in Epileptics With Psychosis** ..... October 425
G. Donald Niswander and Earl K. Holt

**Ritalin and Serpasil Therapy in Chronic Psychoses** ..... March 122
John C. Saunders and Nathan S. Kline

**Schizophrenia As a World Problem** ..... December 513
James L. McCartney

**Scopolamine—Acute Toxic Psychosis Due to** ..... October 423
Laurence R. Mundy and William W. Zeller

**Sleep Treatment in Mental Disorders** ..... December 523
H. Azima

**Suicidal Risk in a Municipal General Hospital** ..... December 556
Jacob H. Friedman and Remo Cancellieri

**Succinylcholine Chloride Technics** ..... Supp. July 72

**Sustained-Release Psychopharmacologic Agents in Psychiatric Treatment** ..... October 431
Marks G. Jacoby, Oscar Pelzman and H. Babikian

**Symposium on Conventional Electric Shock Therapy—Introduction** ..... October 435
John D. Moriarty

**Taraxein and LSD—Mode of Action** ..... November 478
B. Melander and S. Martens

**Teaching As Training for Psychiatric Residents** ..... June 245
Marietta Houston and David W. Allen

**Thiobarbiturates and Electroshock Therapy** ..... July 295
Edward F. Kerman

**Thorazine Photosensitivity** ..... June 264
E. M. Caffey, Jr., James E. Lindeman and Alfred S. Roberts

**Thorazine Therapy—Early and Late Response** ..... September 399
Peter Conran

**Thyroid Function in Mental Diseases** ..... August 338
John D. Stevens and Arthur L. Dunn

**Thyroid Therapy of Schizophrenia** ..... September 373
Lawis Danziger

**Tranquilizing Medication—Chronic Patients' Comments** ..... May 214
B. J. Bolin

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